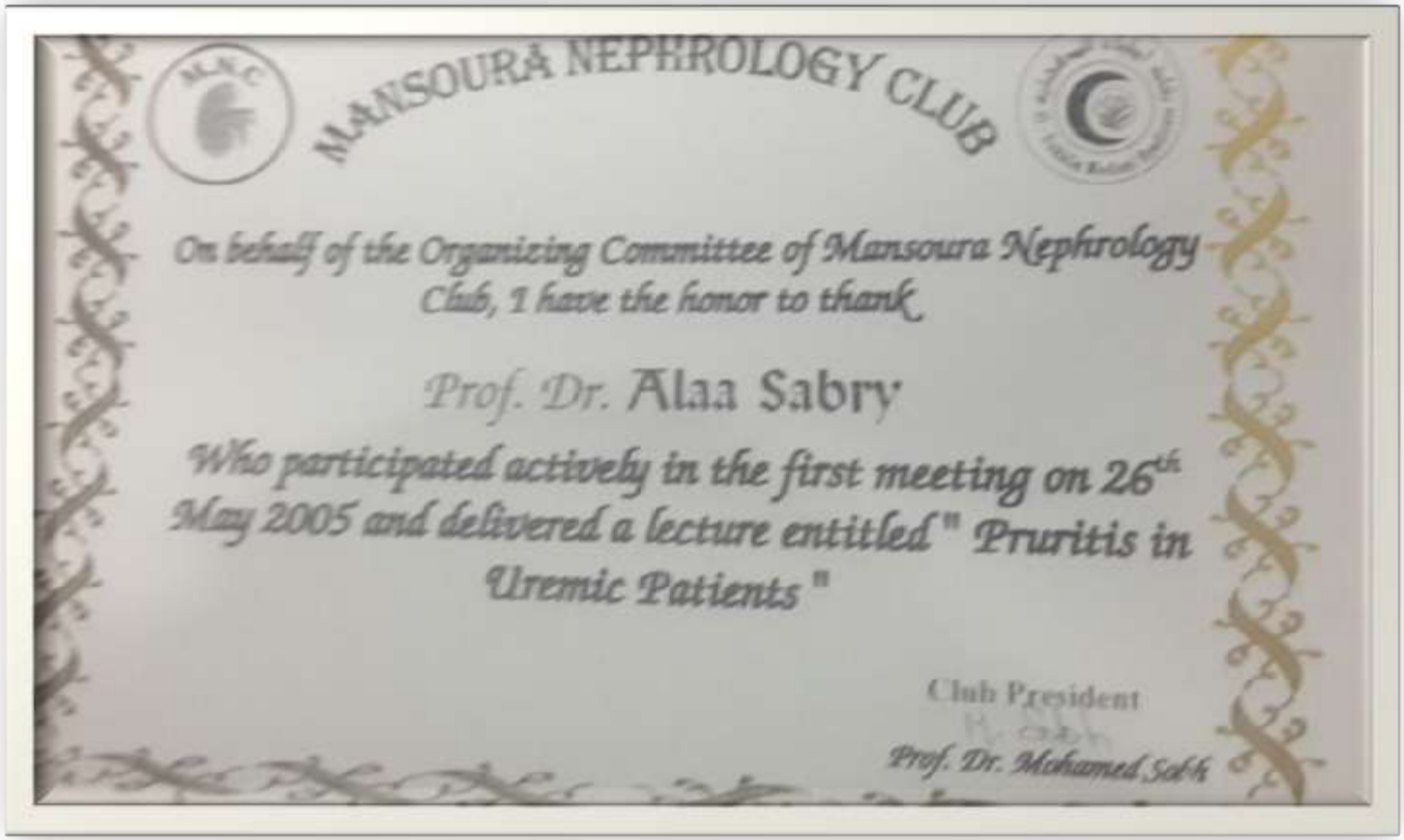
MEMORIES



MANSOURA NEPHROLOGY CLUB

On behalf of the Organizing Committee of Mansoura Nephrology Club, I have the honor to thank

Prof. Dr. Alaa Sabry

Who participated actively in the first meeting on 26th May 2005 and delivered a lecture entitled " Pruritis in Uremic Patients "

Club President

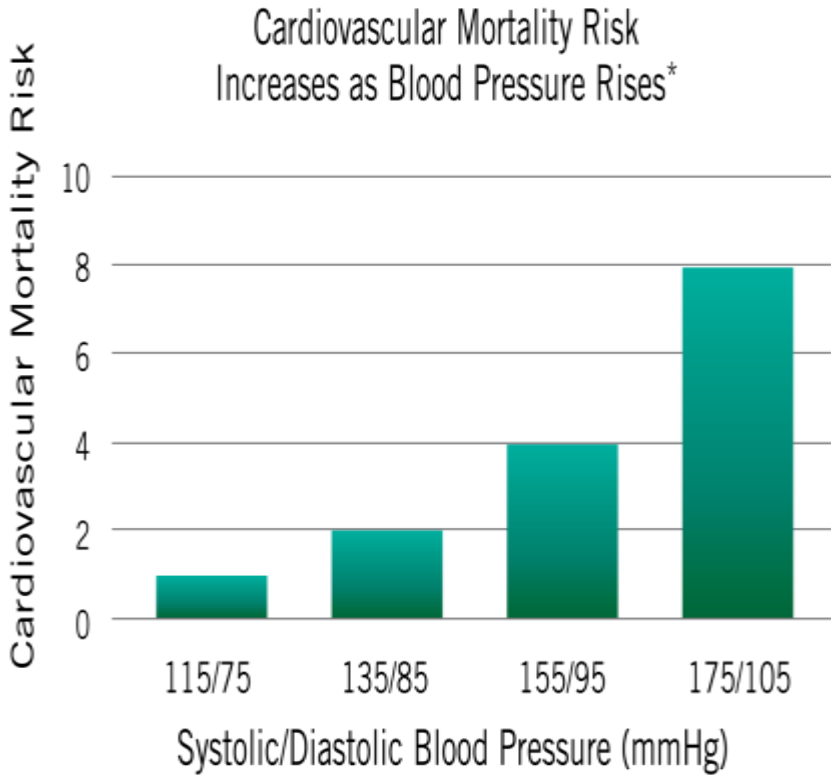
Prof. Dr. Mohamed Sobh

Hypertension remains a major global public health burden.

An estimated 30–40% of the adult population in the developed world suffer from this condition.

Every 20/10 mmHg increase in BP correlates with a doubling of 10-yearcardiovascular mortality

Only half of all treated hypertensives are controlled to established BP targets



Lewington et al. 2002[2]

Sarafidis PA, Bakris GL. *J Am Coll Cardiol*. 2008.

Resistant Hypertension

- **Failure to reach BP goal despite using at least three antihypertensive medications in adequate dosages (including at least one diuretic):**
  - **Office: ≤ 140/90 mmHg or ≤ 130/80mmHg (in DM & CKD)**
  - **ABPM: Daytime < 135/85 mmHg, nighttime < 120/70 mmHg**
  - **Using ≥ 4 drugs, independent of BP control, can also be diagnosed as RH.**

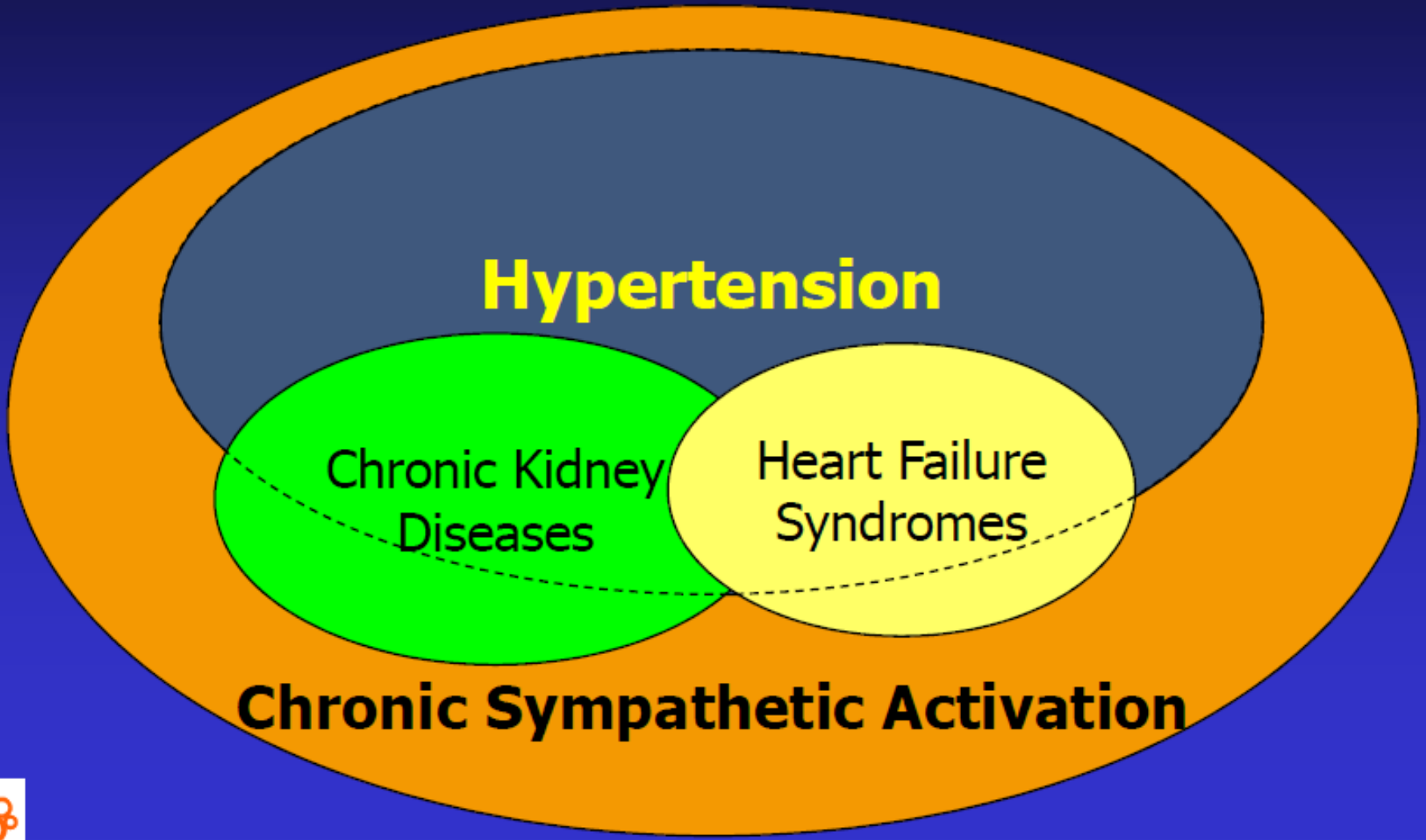
Calhoun et al., Hypertension 2008; 51: 1403–1419

- **Lack of nocturnal decrease of blood pressure ("non-dipper") in 24-hour ABPM is considered by some to be resistant.**

- **10% of patients with diagnosed hypertension have resistant hypertension.**

Rios et al., Chronobiol Int 2013; 30: 207–20

Interrelationship of Heart & Kidney Disease

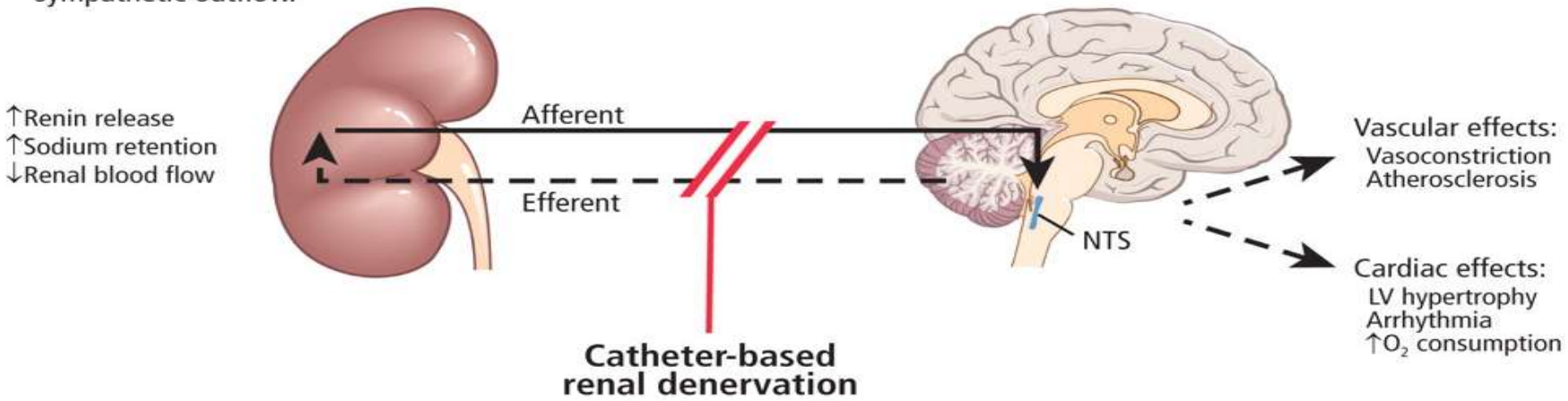


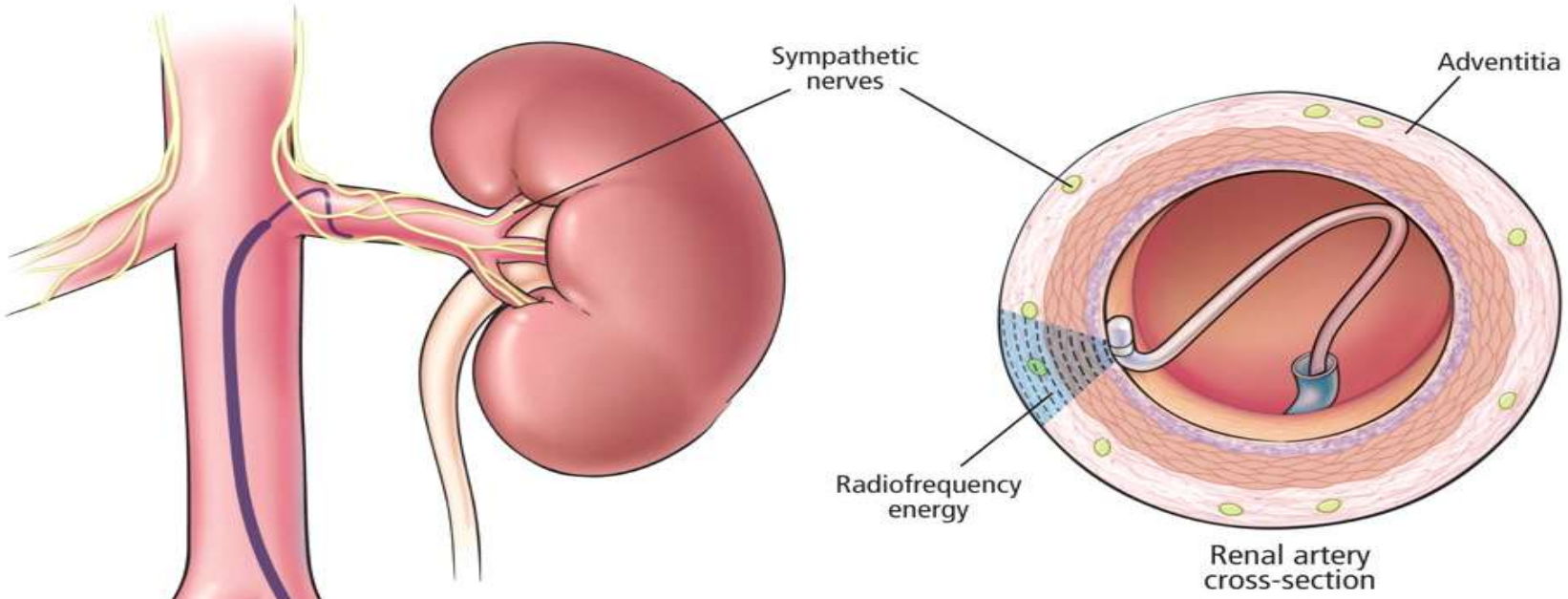
Device-Based Therapy

- A- Renal Denervation (RD).
- B-Baro Receptor Activation(BAT).
- C-Central arteriovenous anastomosis.

Kidneys, in response to ischemia, send afferent sympathetic signals to the brain that disinhibit the nuclei tractus solitarii (NTS), increasing sympathetic outflow.

The NTS in the brainstem control efferent sympathetic signals from the brain to various organs of the body. Sympathetic signals raise blood pressure by increasing the heart rate, constricting arteries, and, in the kidney, increasing renin release and sodium and fluid retention.





In the renal denervation procedure, a specially designed catheter is positioned in the renal artery, and radiofrequency energy is applied to the endoluminal surface.

Surgical History

THE EFFECTS OF PROGRESSIVE SYMPATHECTOMY ON BLOOD PRESSURE

BRADFORD CANNON

From the Laboratories of Physiology in the Harvard Medical School

Received for publication March 24, 1931

Dr. Reginald H. Smithwick

THE EFFECT OF RENAL DENERVATION ON THE LEVEL OF ARTERIAL BLOOD PRESSURE AND RENAL FUNCTION IN ESSENTIAL HYPERTENSION

By IRVINE H. PAGE and GEORGE J. HEUER

(From the Hospital of the Rockefeller Institute for Medical Research, New York, and the Department of Surgery, New York Hospital, New York)

(Received for publication September 12, 1934)

THE JOURNAL

of the American Medical Association

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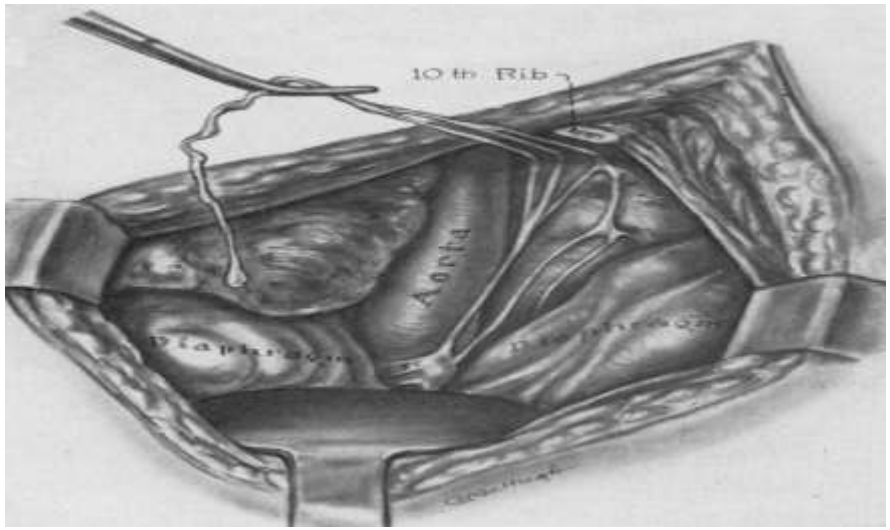
VOL. 152, NO. 16 — CHICAGO, ILLINOIS — AUGUST 15, 1953

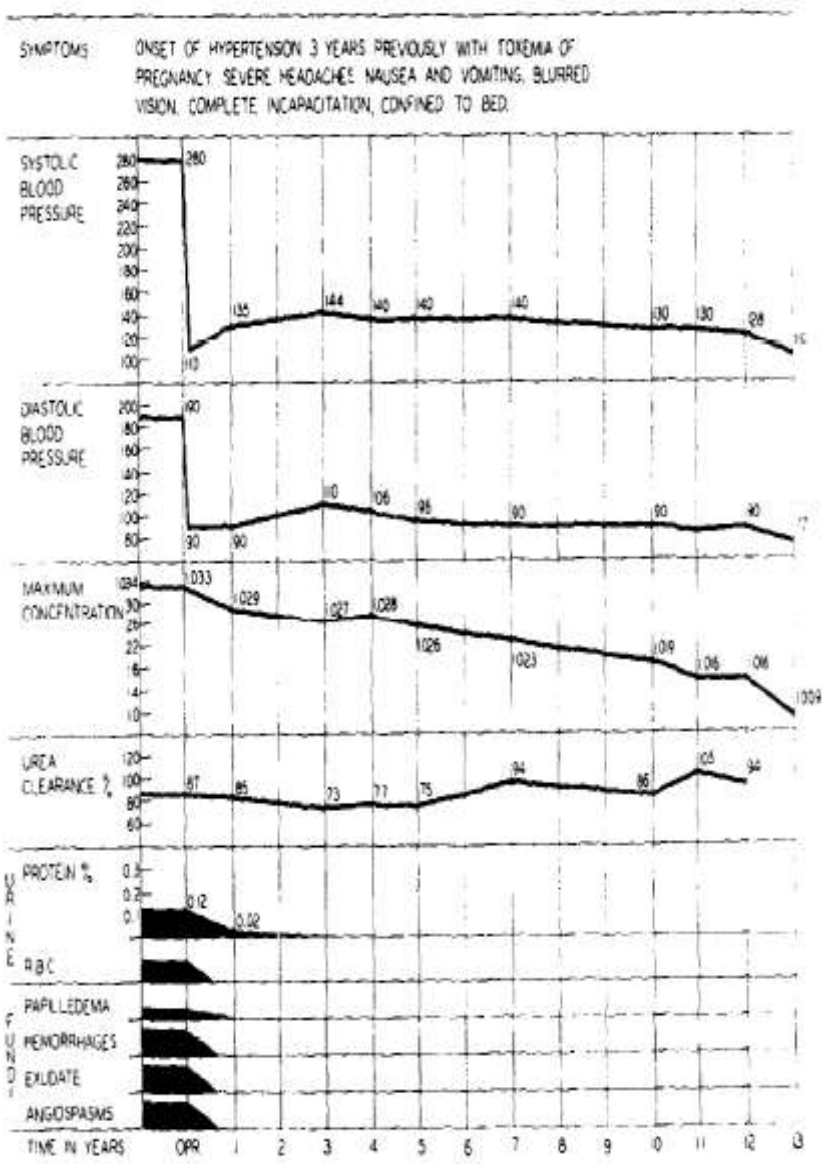
SPLANCHNICECTOMY FOR ESSENTIAL HYPERTENSION

RESULTS IN 1,266 CASES

Reginald H. Smithwick, M.D.
and
Jesse E. Thompson, M.D., Boston

Surgical Sympathectomy

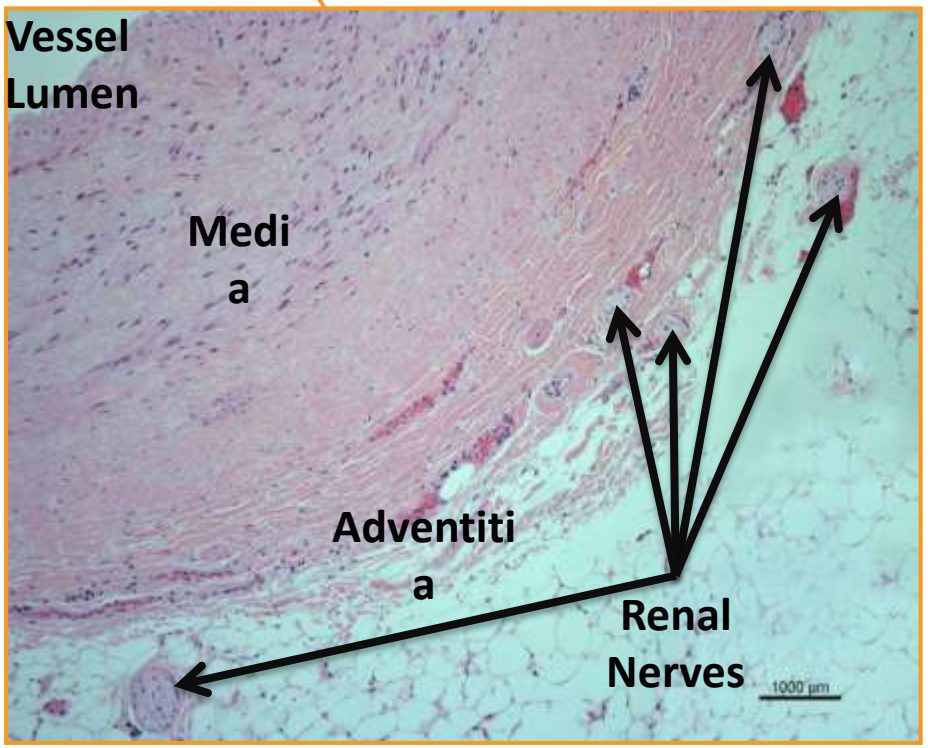




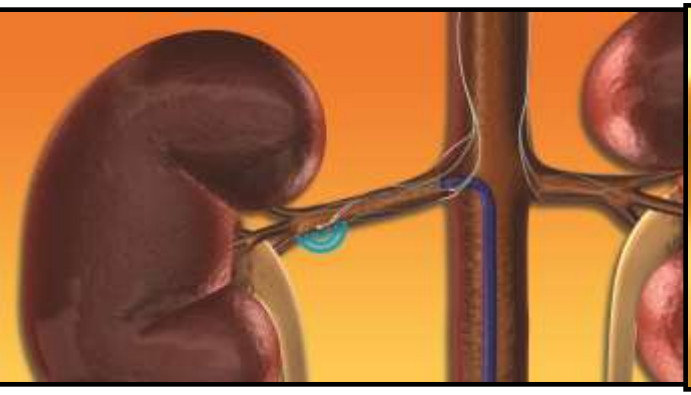
Grimson, Ann Surg 1941

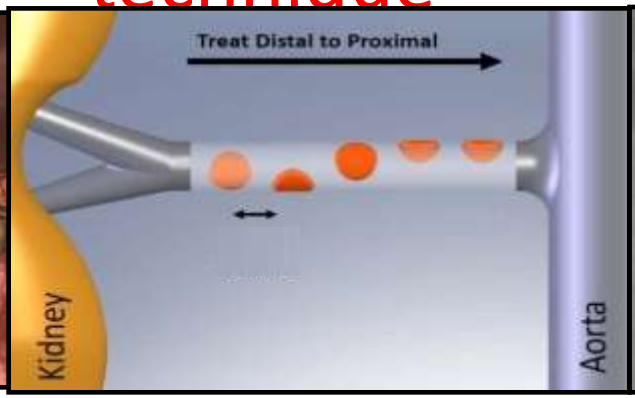
- The Symplicity system is the name of a series of trials sponsored by the Medtronic company that are evaluating the efficacy and safety of therapy with a renal denervation catheter for a variety of problems, but most importantly for hypertension.

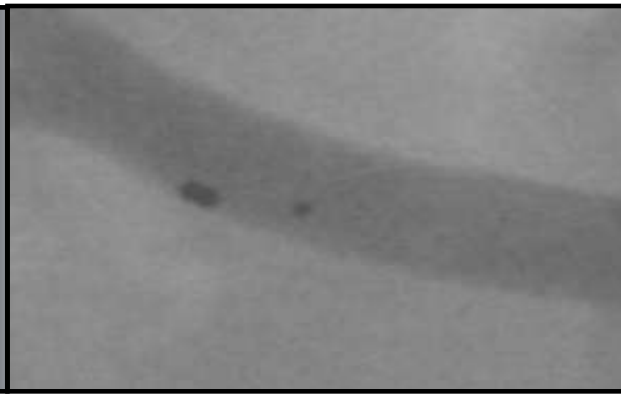
- launched in Europe in 2010 and is also currently available in Asia, Africa, Australia, and Canada. No renal denervation system has yet been approved in the United States.



Catheter-Based Approach technique







Renal artery access via standard interventional

4-6 two-minute treatments per artery

Proprietary RF generator

Automated

Low power (Released Energy maximum 8 Watt)

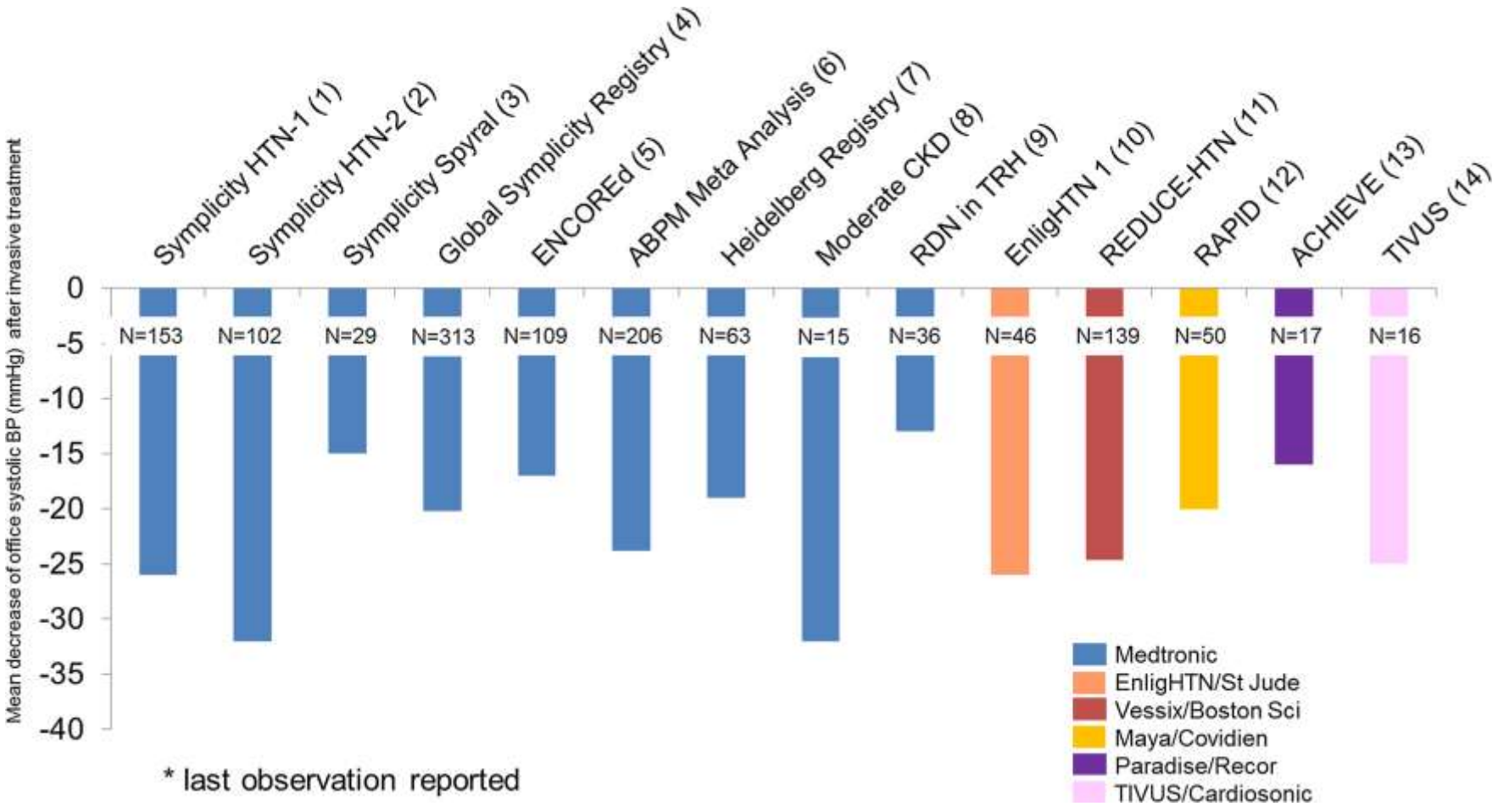
Built-in safety algorithms

Temperature between 40-75 °

The generator automatically switch of if

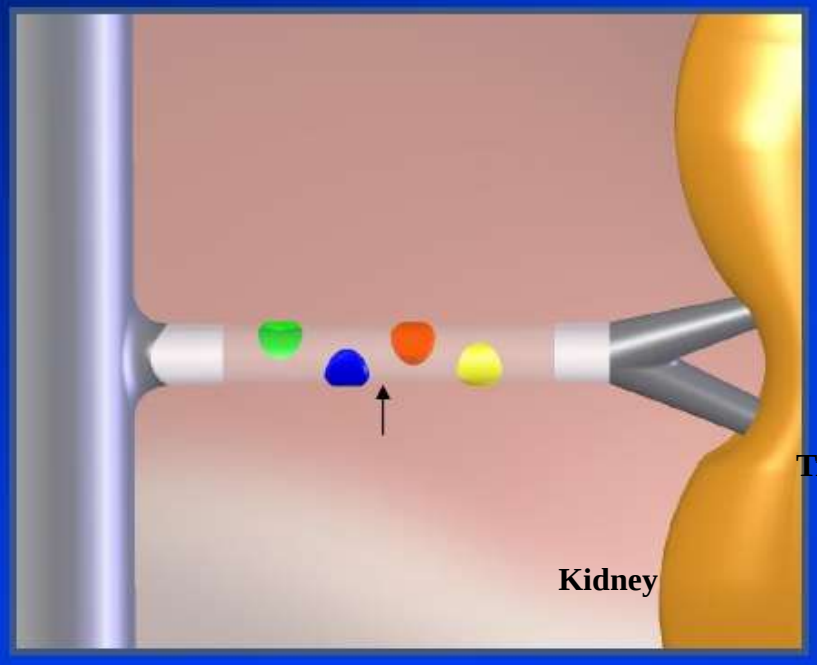
Temperature is higher than 75 °

Five renal denervation catheter systems



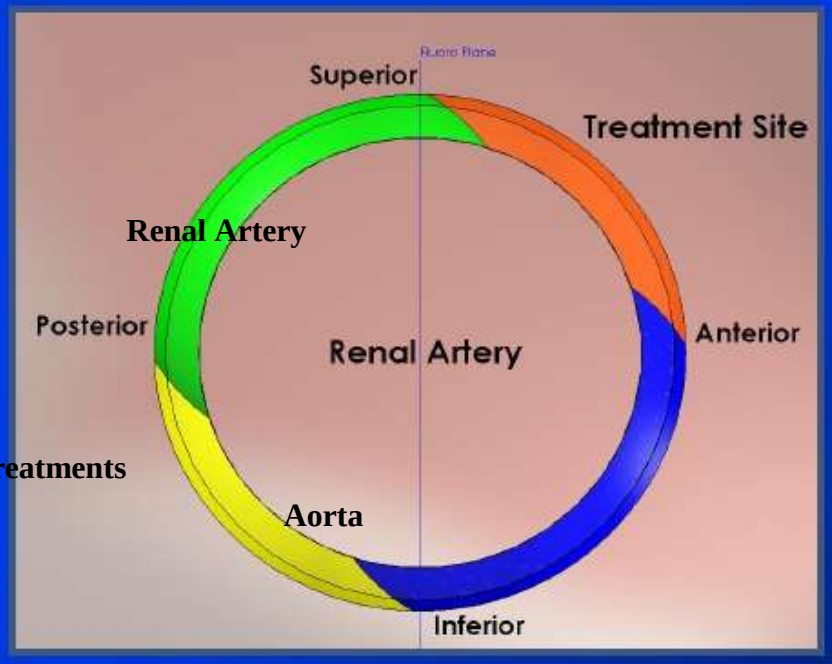
Ott et al., Curr Hypertens Rep (2014) 16:488

Treatment Strategy



Focal ablations

spaced along vessel



Treatments

Multiple focal ablations

↑ circumferential coverage

Catheter-based renal sympathetic denervation for resistant hypertension: a multicentre safety and proof-of-principle cohort study

Henry Krum, Markus Schlaich, Rob Whitbourn, Paul A Sobotka, Jerzy Sadowski, Krzysztof Bartus, Boguslaw Kapelak, Anthony Walton, Horst Sievert, Suku Thambar, William T Abraham, Murray Esler

Summary

Background Renal sympathetic hyperactivity is associated with hypertension and its progression, chronic kidney disease, and heart failure. We did a proof-of-principle trial of therapeutic renal sympathetic denervation in patients with resistant hypertension (ie, systolic blood pressure ≥160 mm Hg on three or more antihypertensive medications, including a diuretic) to assess safety and blood-pressure reduction effectiveness.

Methods We enrolled 50 patients at five Australian and European centres; 5 patients were excluded for anatomical reasons (mainly on the basis of dual renal artery systems). Patients received percutaneous radiofrequency catheter-based treatment between June, 2007, and November, 2008, with subsequent follow-up to 1 year. We assessed the effectiveness of renal sympathetic denervation with renal noradrenaline spillover in a subgroup of patients. Primary endpoints were office blood pressure and safety data before and at 1, 3, 6, 9, and 12 months after procedure. Renal angiography was done before, immediately after, and 14–30 days after procedure, and magnetic resonance angiogram 6 months after procedure. We assessed blood-pressure lowering effectiveness by repeated measures ANOVA. This study is registered in Australia and Europe with ClinicalTrials.gov, numbers NCT 00483808 and NCT 00664638.

Findings In treated patients, baseline mean office blood pressure was 177/101 mm Hg (SD 20/15), (mean 4·7 antihypertensive medications); estimated glomerular filtration rate was 81 mL/min/1·73m² (SD 23); and mean reduction in renal noradrenaline spillover was 47% (95% CI 28–65%). Office blood pressures after procedure were reduced by −14/−10, −21/−10, −22/−11, −24/−11, and −27/−17 mm Hg at 1, 3, 6, 9, and 12 months, respectively. In the five non-treated patients, mean rise in office blood pressure was +3/−2, +2/+3, +14/+9, and +26/+17 mm Hg at 1, 3, 6, and 9 months, respectively. One intraprocedural renal artery dissection occurred before radiofrequency energy delivery, without further sequelae. There were no other renovascular complications.

Interpretation Catheter-based renal denervation causes substantial and sustained blood-pressure reduction, without serious adverse events, in patients with resistant hypertension. Prospective randomised clinical trials are needed to investigate the usefulness of this procedure in the management of this condition.

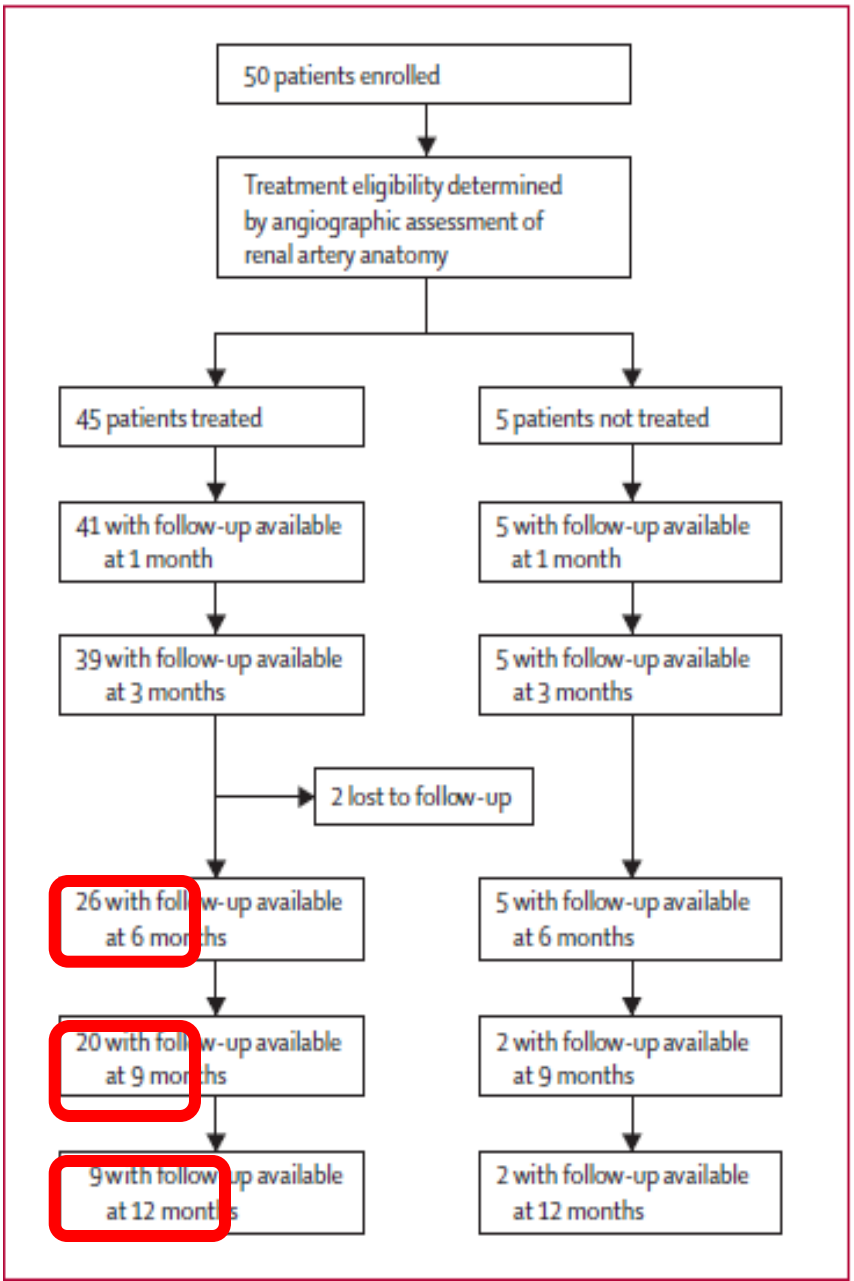
Funding Ardian Inc.

Lancet 2009; 373: 1275–81
Published Online
March 30, 2009
DOI:10.1016/S0140-6736(09)60566-3

See Comment page 1228

Centre of Cardiovascular Research and Education in Therapeutics, Department of Epidemiology and Preventive Medicine, Monash University, Melbourne, VIC, Australia (Prof H Krum PhD); **Baker IDI Heart and Diabetes Institute, Melbourne, VIC, Australia** (M Schlaich MD, Prof M Esler MBBS); **St Vincent's Hospital, Melbourne, VIC, Australia** (R Whitbourn MBBS); **Ardian Inc, Palo Alto, CA, USA** (P A Sobotka MD); **The Ohio State University, Columbus, OH, USA** (P A Sobotka, Prof W T Abraham MD); **Jagiellonian University, Krakow, Poland** (Prof J Sadowski MD, K Bartus MD, B Kapelak MD); **Alfred Hospital, Melbourne, VIC, Australia** (A Walton MBBS, Prof H Krum); **Cardiovascular Centre Frankfurt, Frankfurt, Germany** (Prof H Sievert MD); **and John Hunter Hospital, Newcastle, NSW, Australia**

Trial profile

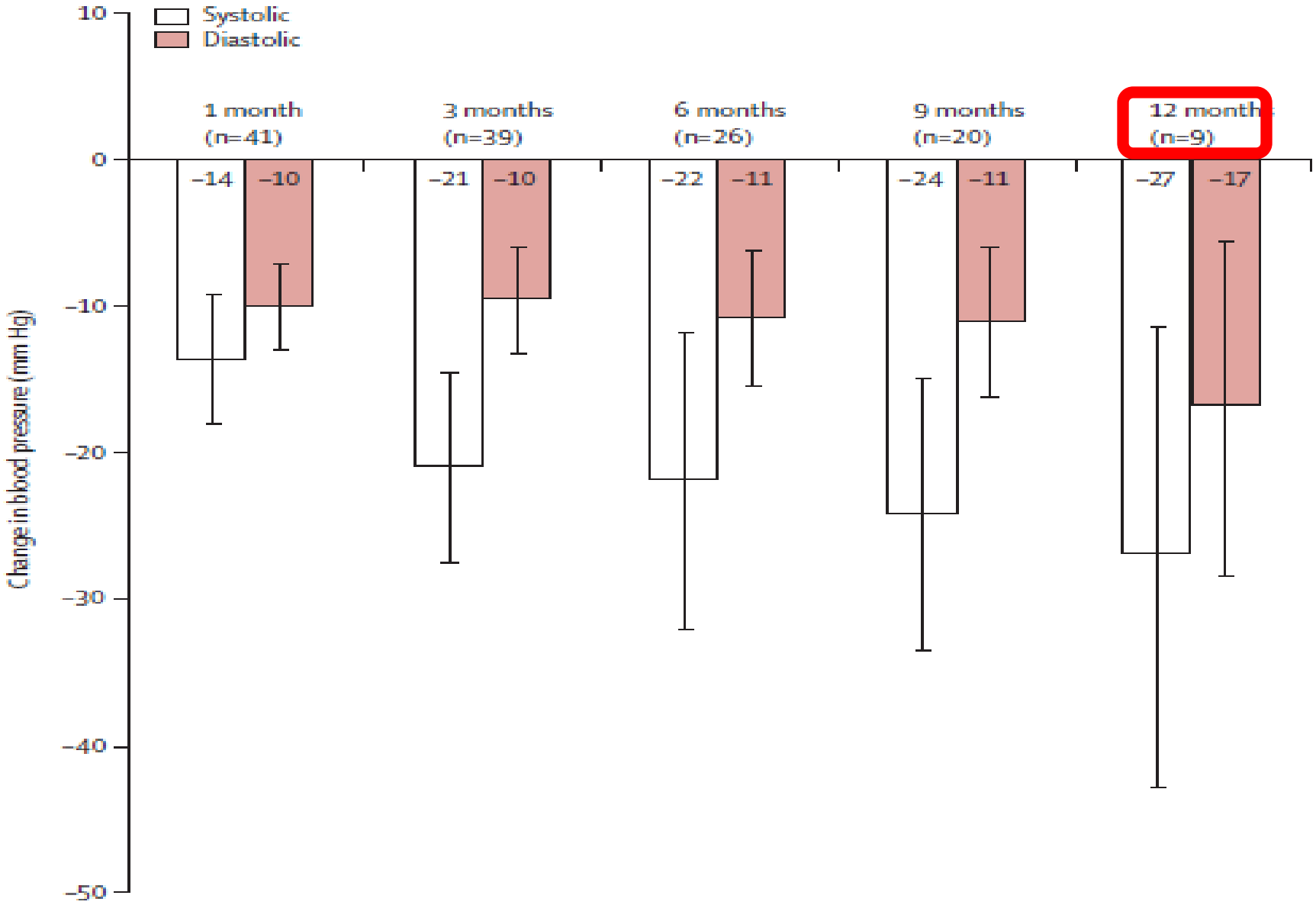


Baseline patient characteristics

	All patients (N=50)	Patients undergoing procedure (N=45)	Patients not eligible for procedure (N=5)
Age (years)	57 (9)	58 (9)	51 (8)
Sex (female)	21 (42%)	20 (44%)	1 (20%)
Ethnic origin (non-white)	2 (4%)	2 (4%)	0
Type 2 diabetes mellitus	16 (32%)	14 (31%)	2 (40%)
CAD	11 (22%)	10 (22%)	1 (20%)
Hyperlipidaemia	34 (68%)	29 (64%)	5 (100%)
eGFR (mL/min/1·73 m^2)	83 (22)	81 (23)	95 (15)
Heart rate (bpm)	73 (11)	72 (11)	79 (9)
Blood pressure (mm Hg)	177/100 (19/14)	177/101 (20/15)	173/98 (8/9)
Number of antihypertension drugs	4·7 (1·4)	4·7 (1·5)	4·6 (0·5)
ACE or ARB	47 (94%)	43 (96%)	4 (80%)
β blocker	39 (78%)	34 (76%)	5 (100%)
Calcium-channel blocker	36 (72%)	31 (69%)	5 (100%)
Vasodilator	8 (16%)	8 (18%)	0%
Diuretic	46 (92%)	43 (96%)	3 (60%)

Data are mean (SD) or number (%). ACE=angiotensin-converting enzyme inhibitor. ARB=angiotensin II receptor blocker. bpm=beats per minute. CAD=coronary artery disease. eGFR=estimated glomerular filtration rate.

Change in office blood pressure



- **Non-response :**
- Six of 45 treated patients (13%) .

(had systolic blood-pressure reductions of less than 10 mm Hg) .

- **Changes in renal noradrenaline spillover :**
- Ten patients .
- The mean reduction in the was 47%.

- **GFR (in 25 patients) :**
- Paired baseline and 6-month follow-up glomerular filtration rate data were available, and were 79 and 83 mL/min/1・73m2 .
- Six of 25 patients (24%) of patients had 20% or more improvement in glomerular filtration rate after the procedure.
- **Safety:**
- Diffuse visceral non-radiating abdominal pain
- Renal artery dissection: 1 patient .
- Pseudoaneurysm at the femoral access site : 1 patient.

Hypertension
Celebrating 30 Years: 1979 to 2009
JOURNAL OF THE AMERICAN HEART ASSOCIATION

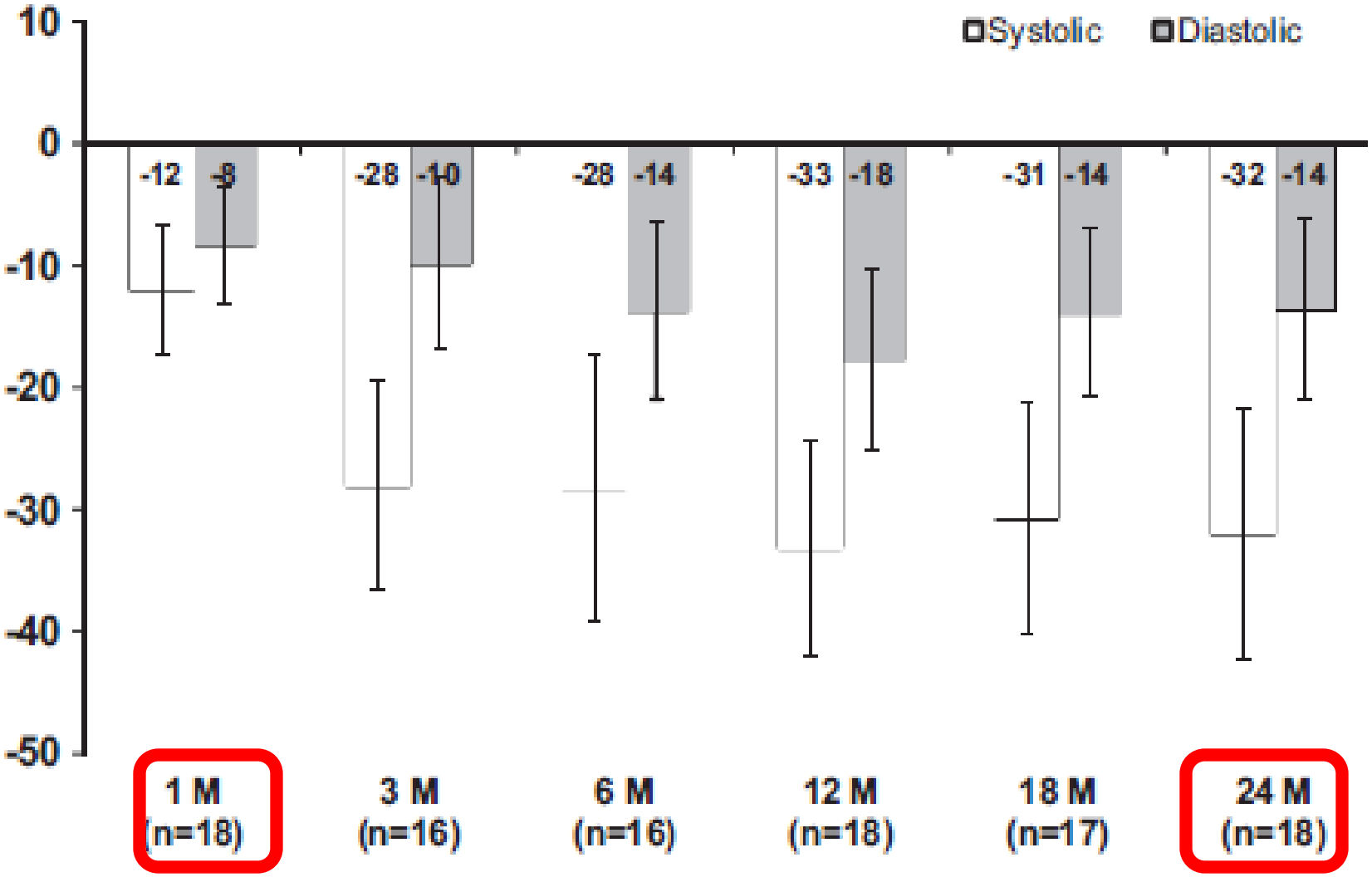
Catheter-Based Renal Sympathetic Denervation for Resistant Hypertension

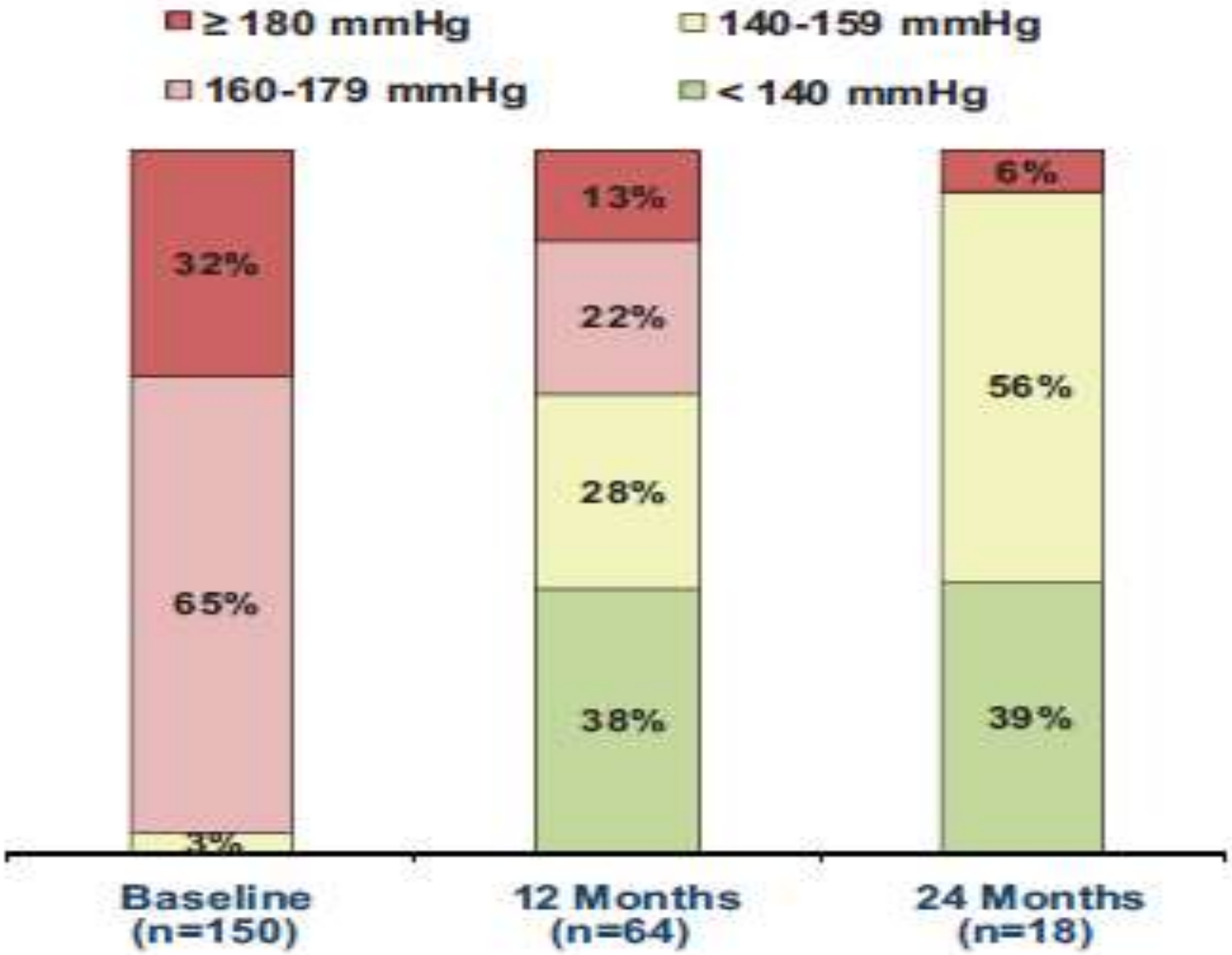
Durability of Blood Pressure Reduction Out to 24 Months

Symplicity HTN-1 Investigators*

Hypertension. 2011;57:911-917.

Systolic and diastolic changes where (*P0.002) at all time points postprocedure with BPs* reduced on average by 20/10, 24/11, 25/11, 23/11, 26/14, and 32/14 mm Hg at 1, 3, 6, 12, 18, and 24 months




≥ 180 mmHg
140-159 mmHg
160-179 mmHg
< 140 mmHg
32%
65%
3%
13%
22%
28%
38%
6%
56%
39%
Baseline (n=150)
12 Months (n=64)
24 Months (n=18)

Baseline Predictors of BP Response

- **Predictors of greater systolic BP response:**
- **Higher baseline systolic BP (*P0.0001) and use of central sympatholytic agents (P0.018).***
- **GFR:**
- **eGFR data were only available on 10 patients at 2 years. In these 10 patients, eGFR changed by - 16.0 mL/min per 1.73 m2 at 24 months postprocedure.**
- **In no cases did serum creatinine double, the patient develop class IV chronic kidney disease (15 to 29 mL/min per 1.73 m2), or the patient require dialysis.**
- ***Death***
- **Two patients died within the follow-up period postprocedure.**
- **Neither death was considered to be related to the device or the procedure.**

Conclusion

- The initial reported BP reduction out to 12 months postrenal sympathetic denervation procedure has now been observed to persist out to 24 months of follow-up postprocedure.
- Hypthesis ??????:
- 1- A predominant procedure with a resetting of central sympathetic outflow.
- 2- A resetting of the baroreflex around a lower homeostatic set point.
- 3- Vascular remodeling may have been reversed over the 24-month period, with that reversal sustained postprocedure.
- Whatever the mechanism, this appears to override any functional reinnervation that may be occurring postprocedure.

Renal sympathetic denervation in patients with treatment-resistant hypertension (The Symplicity HTN-2 Trial): a randomised controlled trial

*Symplicity HTN-2 Investigators**

Lancet 2010; 376: 1903–09
Published Online
November 17, 2010
DOI:10.1016/S0140-6736(10)62039-9

See Comment page 1878

*Members listed at end of paper

Correspondence to:
Prof Murray D Esler, Baker IDI Heart and Diabetes Institute, PO Box 6492, St Kilda Road, Central Melbourne, VIC 8008, Australia
murray.esler@bakeridi.edu.au

Summary

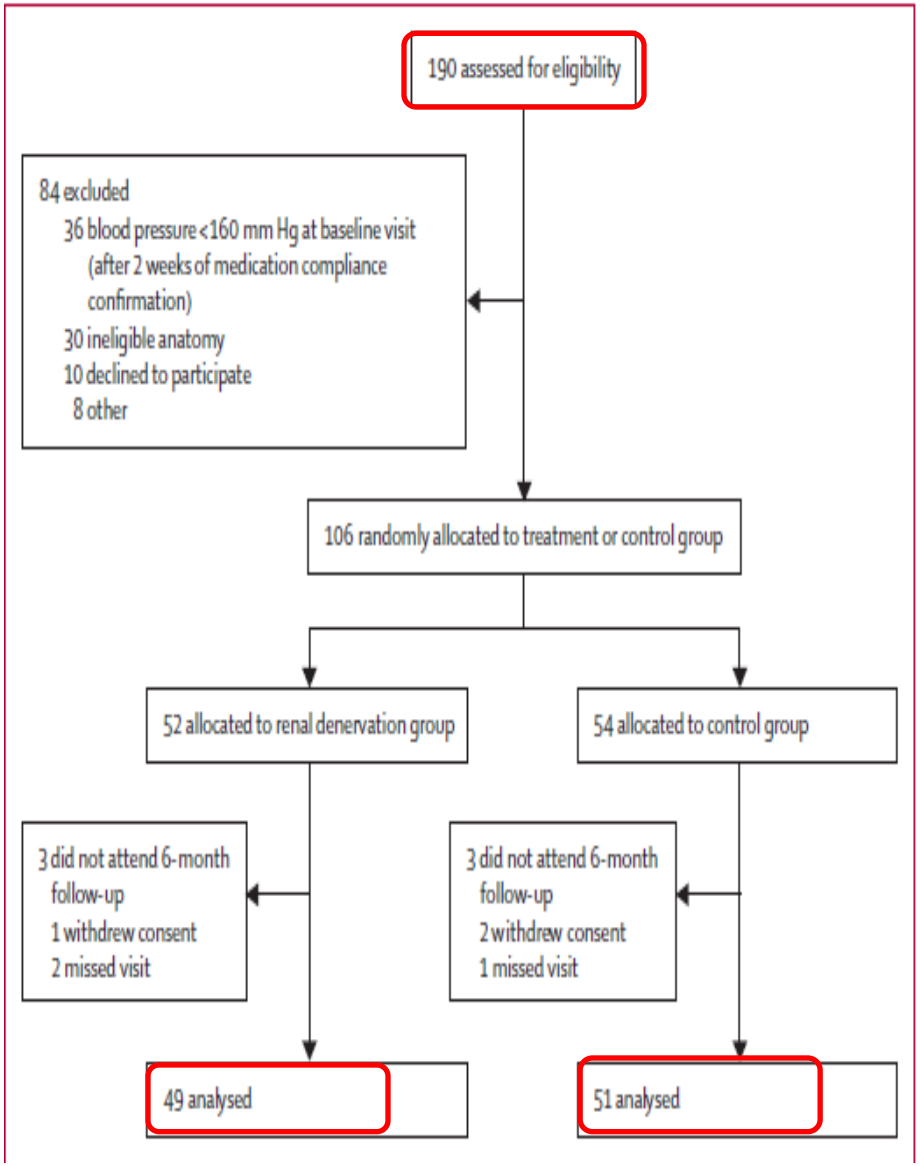
Background Activation of renal sympathetic nerves is key to pathogenesis of essential hypertension. We aimed to assess effectiveness and safety of catheter-based renal denervation for reduction of blood pressure in patients with treatment-resistant hypertension.

Methods In this multicentre, prospective, randomised trial, patients who had a baseline systolic blood pressure of 160 mm Hg or more (≥150 mm Hg for patients with type 2 diabetes), despite taking three or more antihypertensive drugs, were randomly allocated in a one-to-one ratio to undergo renal denervation with previous treatment or to maintain previous treatment alone (control group) at 24 participating centres. Randomisation was done with sealed envelopes. Data analysers were not masked to treatment assignment. The primary effectiveness endpoint was change in seated office-based measurement of systolic blood pressure at 6 months. Primary analysis included all patients remaining in follow-up at 6 months. This trial is registered with ClinicalTrials.gov, number NCT00888433.

Findings 106 (56%) of 190 patients screened for eligibility were randomly allocated to renal denervation (n=52) or control (n=54) groups between June 9, 2009, and Jan 15, 2010. 49 (94%) of 52 patients who underwent renal denervation and 51 (94%) of 54 controls were assessed for the primary endpoint at 6 months. Office-based blood pressure measurements in the renal denervation group reduced by 32/12 mm Hg (SD 23/11, baseline of 178/96 mm Hg, p<0·0001), whereas they did not differ from baseline in the control group (change of 1/0 mm Hg [21/10], baseline of 178/97 mm Hg, p=0·77 systolic and p=0·83 diastolic). Between-group differences in blood pressure at 6 months were 33/11 mm Hg (p<0·0001). At 6 months, 41 (84%) of 49 patients who underwent renal denervation had a reduction in systolic blood pressure of 10 mm Hg or more, compared with 18 (35%) of 51 controls (p<0·0001). We noted no serious procedure-related or device-related complications and occurrence of adverse events did not differ between groups; one patient who had renal denervation had possible progression of an underlying atherosclerotic lesion, but required no treatment.

Interpretation Catheter-based renal denervation can safely be used to substantially reduce blood pressure in treatment-resistant hypertensive patients.

Trial profile



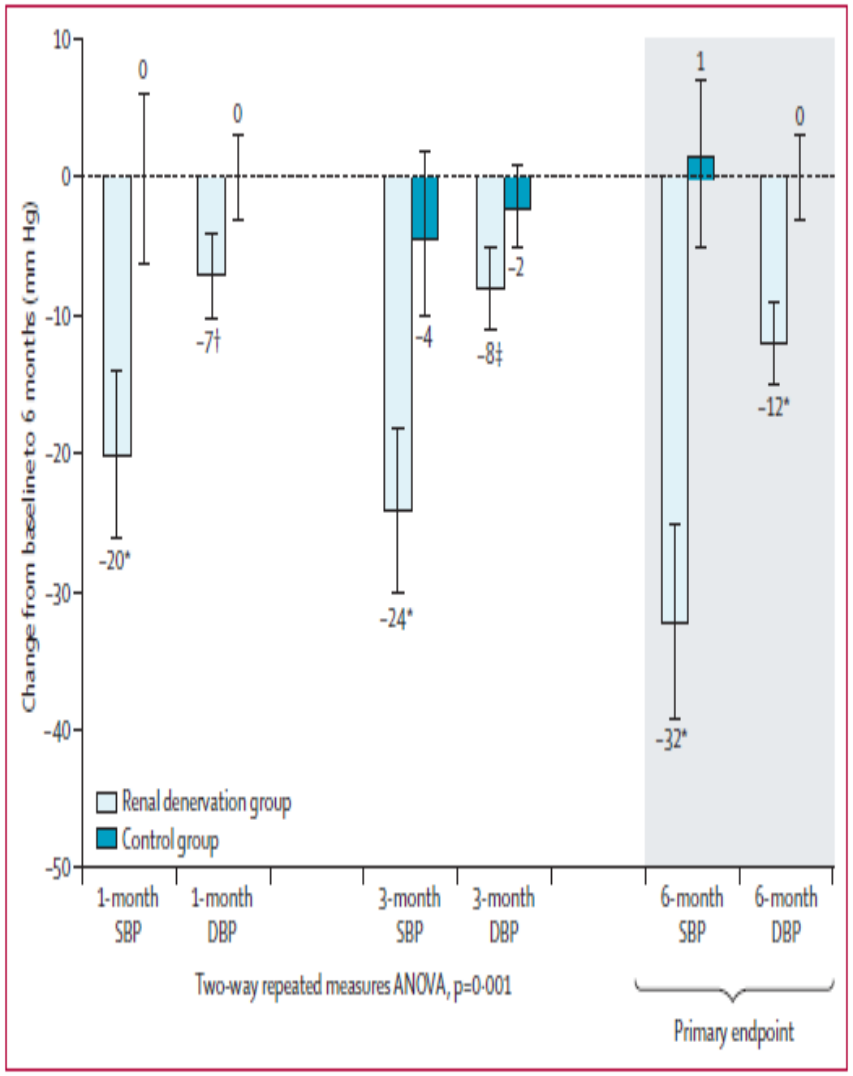
Baseline clinical characteristics, demographics, and background medications for participants

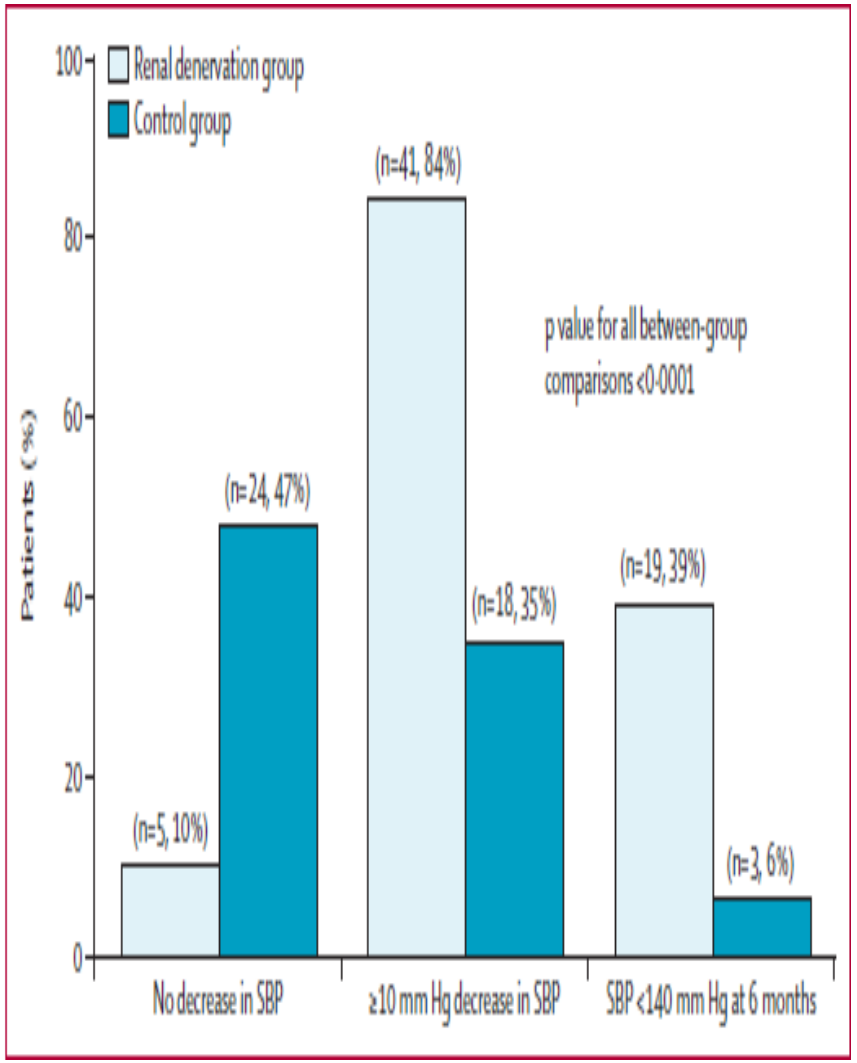
	Renal denervation group (n=52)	Control group (n=54)
Baseline systolic blood pressure (mm Hg)	178 (18)	178 (16)
Baseline diastolic blood pressure (mm Hg)	97 (16)	98 (17)
Age (years)	58 (12)	58 (12)
Sex (female)	18 (35%)	27 (50%)
Race (white)	51 (98%)	52 (96%)
Body-mass index (kg/m²)	31 (5)	31 (5)
Type 2 diabetes	21 (40%)	15 (28%)
Coronary artery disease	10 (19%)	4 (7%)
Hypercholesterolaemia	27 (52%)	28 (52%)
eGFR* (mL/min per 1·73 m²)	77 (19)	86 (20)
eGFR* 45–60 mL/min per 1·73 m²	11 (21%)	6 (11%)
Serum creatinine (μmol/L)	91 (25)	78 (18)
Urine albumin-to-creatinine ratio (mg/g)†	128 (363)	109 (254)
Cystatin C (mg/L)‡	0·9 (0·2)	0·8 (0·2)
Heart rate (bpm)	75 (15)	71 (15)
Number of antihypertension medications	5·2 (1·5)	5·3 (1·8)
Patients on hypertension medication for more than 5 years	37 (71%)	42 (78%)
Patients on five or more medications	35 (67%)	31 (57%)
Patients receiving (drug class)		
ACE inhibitors/ARBs	50 (96%)	51 (94%)
Direct renin inhibitors	8 (15%)	10 (19%)
β blockers	43 (83%)	37 (69%)
Calcium-channel blockers	41 (79%)	45 (83%)
Diuretics	46 (89%)	49 (91%)
Aldosterone antagonist	9 (17%)	9 (17%)
Vasodilators	8 (15%)	9 (17%)
α-1 blockers	17 (33%)	10 (19%)
Centrally acting sympatholytics	27 (52%)	28 (52%)

Data are mean (SD) or number (%). eGFR=estimated glomerular filtration rate. ACE=angiotensin-converting enzyme. ARB=angiotensin-receptor blocker. *Calculated on the basis of Modification of Diet in Renal Disease Study criteria.[32] †42 participants in the renal denervation group and 43 participants in the control group used for between-group comparisons with the Wilcoxon rank-sum test for two independent samples. ‡39 participants in the renal denervation group and 42 participants in the control group had data for cystatin C available at baseline.

Renal denervation led to a reduction in blood pressure of 10 mm Hg or more in 84% of treated patients.

(office-based measurements)





Renal Function

	Renal denervation group		Control group		Difference in mean change (95% CI)	p value
	Patients (n)	Mean change (SD)	Patients (n)	Mean change (SD)		
eGFR* (mL/min per 1·73 m²)	49	0·2 (11)	51	0·9 (12)	-0·7 (-5·4 to 3·9)	0·76
Serum creatinine (μmol/L)	49	0·2 (17·6)	51	-1·1 (10·3)	1·3 (-4·5 to 7·0)	0·67
Cystatin C (mg/L)	37	0·1 (0·2)	40	0·0 (0·1)	0·0 (0·0 to 0·1)	0·31

eGFR=estimated glomerular filtration rate. *Calculated on the basis of Modification of Diet in Renal Disease Study criteria.[17]

Table 2: Baseline, change from baseline to 6 months, and difference in change in measured concentrations of eGFR, serum creatinine, and cystatin C for renal denervation and control groups

NO changes in measured renal function with denervation, suggesting that the procedure itself and associated haemodynamic changes have no adverse effects on the kidneys.

Hypertension treatment for people with resistant hypertension

Recommendations	Additonal considerations
Withdraw any drugs in antihypetensive treatment regimen that have absent or minimal effect	
Consider mineralocorticoid receptor antagonists, amiloride, and the alpha-1-blocker doxazosin should be considered (if no contraindication exists)	• *If no contraindications exist*
Invasive approaches: renal denervation and baroreceptor stimulation may be considered	• If drug treatment ineffective
No long-term efficay, safety data for renal denervation, baroreceptor stimulation – only experienced clinicians should use ***Diagnosis and follow-up should be restricted to hypertension Centres***	
Invasive approaches only for truly resistant hypertensive patients	• Clinic values: SBP ≥160 mmHg or DBP ≥110 mmHg with BP elevation confirmed by ABPM

SBP, systolic blood pressure; DBP, diastolic blood pressure; BP, blood pressure.

Conclusion

- Catheter-based renal denervation, done in a multicentre, randomised trial in patients with treatment-resistant essential hypertension, resulted in significant reductions in BP.

- The magnitude of BP reduction can be predicted to affect the development of hypertension-related diseases and mortality.

- The technique was applied without major complications.

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

A Controlled Trial of Renal Denervation for Resistant Hypertension

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N ENGL J MED 370;15 NEJM.ORG APRIL 10, 2014

ABSTRACT

BACKGROUND

Prior unblinded studies have suggested that catheter-based renal-artery denervation reduces blood pressure in patients with resistant hypertension.

METHODS

We designed a prospective, single-blind, randomized, sham-controlled trial. Patients with severe resistant hypertension were randomly assigned in a 2:1 ratio to undergo renal denervation or a sham procedure. Before randomization, patients were receiving a stable antihypertensive regimen involving maximally tolerated doses of at least three drugs, including a diuretic. The primary efficacy end point was the change in office systolic blood pressure at 6 months; a secondary efficacy end point was the change in mean 24-hour ambulatory systolic blood pressure. The primary safety end point was a composite of death, end-stage renal disease, embolic events resulting in end-organ damage, renovascular complications, or hypertensive crisis at 1 month or new renal-artery stenosis of more than 70% at 6 months.

RESULTS

A total of 535 patients underwent randomization. The mean (±SD) change in systolic blood pressure at 6 months was −14.13±23.93 mm Hg in the denervation group as compared with −11.74±25.94 mm Hg in the sham-procedure group ($P<0.001$ for both comparisons of the change from baseline), for a difference of −2.39 mm Hg (95% confidence interval [CI], −6.89 to 2.12; $P=0.26$ for superiority with a margin of 5 mm Hg). The change in 24-hour ambulatory systolic blood pressure was −6.75±15.11 mm Hg in the denervation group and −4.79±17.25 mm Hg in the sham-procedure group, for a difference of −1.96 mm Hg (95% CI, −4.97 to 1.06; $P=0.98$ for superiority with a margin of 2 mm Hg). There were no significant differences in safety between the two groups.

CONCLUSIONS

This blinded trial did not show a significant reduction of systolic blood pressure in patients with resistant hypertension 6 months after renal-artery denervation as compared with a sham control. (Funded by Medtronic; SYMPLICITY HTN-3 ClinicalTrials.gov number, NCT01418261.)

Table 1. Baseline Characteristics of the Study Population.*

Characteristic	Renal-Denervation Group (N=364)	Sham-Procedure Group (N=171)
Age — yr	57.9±10.4	56.2±11.2
Male sex — no. (%)	215 (59.1)	110 (64.3)
Body-mass index†	34.2±6.5	33.9±6.4
Race — no./total no. (%)‡		
Black	90/363 (24.8)	50/171 (29.2)
White	265/363 (73.0)	119/171 (69.6)
Asian	2/363 (0.6)	0/171
Other	6/363 (1.7)	2/171 (1.2)
Medical history — no. (%)		
Renal insufficiency§	34 (9.3)	17 (9.9)
Renal-artery stenosis	5 (1.4)	4 (2.3)
Obstructive sleep apnea	94 (25.8)	54 (31.6)
Stroke	29 (8.0)	19 (11.1)
Transient ischemic attack	28 (7.7)	13 (7.6)
Peripheral artery disease	19 (5.2)	5 (2.9)
Cardiac disease		
Coronary artery disease	101 (27.7)	43 (25.1)
Myocardial infarction	32 (8.8)	11 (6.4)
Diabetes		
Type 1	0	0
Type 2	171 (47.0)	70 (40.9)
Hyperlipidemia — no. (%)	252 (69.2)	111 (64.9)
Current smoker — no. (%)	36 (9.9)	21 (12.3)
Family history of hypertension — no./total no. (%)	305/361 (84.5)	140/170 (82.4)
Hypertension history — no. (%)		
Hospitalization for hypertensive crisis	83 (22.8)	38 (22.2)
Hospitalization for hypotension	8 (2.2)	4 (2.3)
No. of antihypertensive medications	5.1±1.4	5.2±1.4

Table 1. (Continued.)

Characteristic	Renal-Denervation Group (N=364)	Sham-Procedure Group (N=171)
Type of antihypertensive medication — no. (%)		
ACE inhibitor		
Patients taking medication	179 (49.2)	71 (41.5)
Patients taking maximally tolerated dose	167 (45.9)	64 (37.4)
Angiotensin-receptor blocker		
Patients taking medication	182 (50.0)	91 (53.2)
Patients taking maximally tolerated dose	180 (49.5)	88 (51.5)
Aldosterone antagonist	82 (22.5)	49 (28.7)
Alpha-adrenergic blocker	40 (11.0)	23 (13.5)
Beta-blocker	310 (85.2)	147 (86.0)
Calcium-channel blocker		
Patients taking medication	254 (69.8)	125 (73.1)
Patients taking maximally tolerated dose	208 (57.1)	109 (63.7)
Centrally acting sympatholytic agent	179 (49.2)	75 (43.9)
Direct-acting renin inhibitor	26 (7.1)	12 (7.0)
Direct-acting vasodilator	134 (36.8)	77 (45.0)
Diuretic		
Patients taking medication	363 (99.7)	171 (100)
Patients taking maximally tolerated dose	351 (96.4)	167 (97.7)

A total of 1441 patients were assessed for eligibility; of these patients, 535 were enrolled in the trial between October 2011 and May 2013.

Results

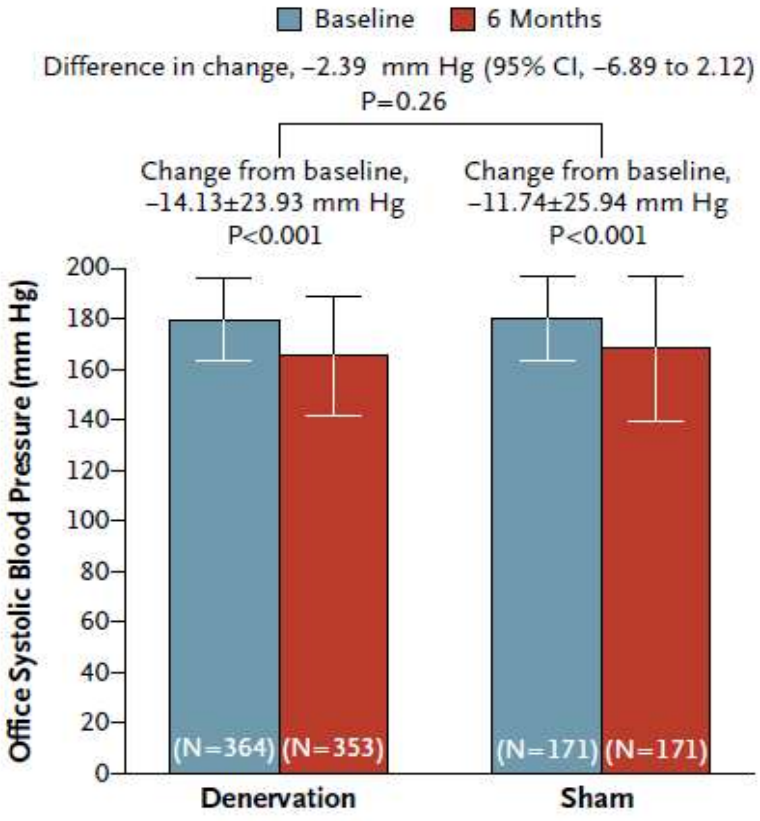


Figure 1. Primary Efficacy End Point.

A significant change from baseline to 6 months in office systolic blood pressure was observed in both study groups. The between-group difference (the primary efficacy end point) did not meet a test of superiority with a margin of 5 mm Hg. The I bars indicate standard deviations.

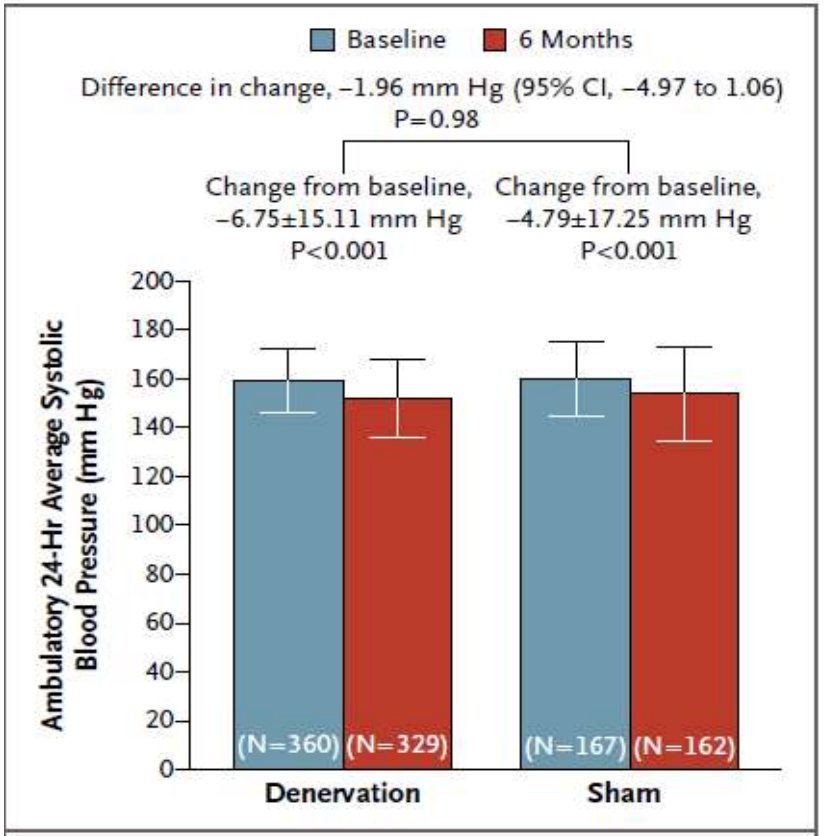


Figure 2. Secondary Efficacy End Point.

A significant change from baseline to 6 months in ambulatory 24-hour average systolic blood pressure was observed in both groups. The between-group difference (the secondary efficacy end point for which the study was powered) did not meet a test of superiority with a margin of 2 mm Hg. The I bars indicate standard deviations.

Primary safety end point

- **There were few major adverse events in the trial: five in the denervation group (1.4%) and one in the sham-procedure group (0.6).**

Table 2. Safety End Points.*

End point	Renal-Denervation Group	Sham-Procedure Group	Percentage-Point Difference (95% CI)
	no. of patients/total no. (%)		
Major adverse event†	5/361 (1.4)	1/171 (0.6)	0.8 (−0.9 to 2.5)
Composite safety end point at 6 mo‡	14/354 (4.0)	10/171 (5.8)	−1.9 (−6.0 to 2.2)
Specific event within 6 mo			
Death	2/352 (0.6)	1/171 (0.6)	0.0 (−1.4 to 1.4)
Myocardial infarction	6/352 (1.7)	3/171 (1.8)	0.0 (−2.4 to 2.3)
New-onset end-stage renal disease	0/352	0/171	—
Increase in serum creatinine of >50% from baseline	5/352 (1.4)	1/171 (0.6)	0.8 (−0.8 to 2.5)
Embolic event resulting in end-organ damage	1/352 (0.3)	0/171	0.3 (−0.3 to 0.8)
Renal-artery intervention	0/352	0/171	—
Vascular complication requiring treatment	1/352 (0.3)	0/171	0.3 (−0.3 to 0.8)
Hypertensive crisis or emergency	9/352 (2.6)	9/171 (5.3)	−2.7 (−6.4 to 1.0)
Stroke	4/352 (1.1)	2/171 (1.2)	0.0 (−2.0 to 1.9)
Hospitalization for new-onset heart failure	9/352 (2.6)	3/171 (1.8)	0.8 (−1.8 to 3.4)
Hospitalization for atrial fibrillation	5/352 (1.4)	1/171 (0.6)	0.8 (−0.8 to 2.5)
New renal-artery stenosis of >70%	1/332 (0.3)	0/165	0.3 (−0.3 to 0.9)

† The primary safety end point was a composite of major adverse events, defined as death from any cause, end-stage renal disease, an embolic event resulting in end-organ damage, renal-artery or other vascular complications, or hypertensive crisis within 30 days or new renal-artery stenosis of more than 70% within 6 months. The objective performance criteri-

- **Kidney function :**
- There were no significant differences between the two groups at any time point

- **Glycated hemoglobin levels :**

- There was no significant between-group difference in the change in glycated hemoglobin levels from baseline to 6 months overall.

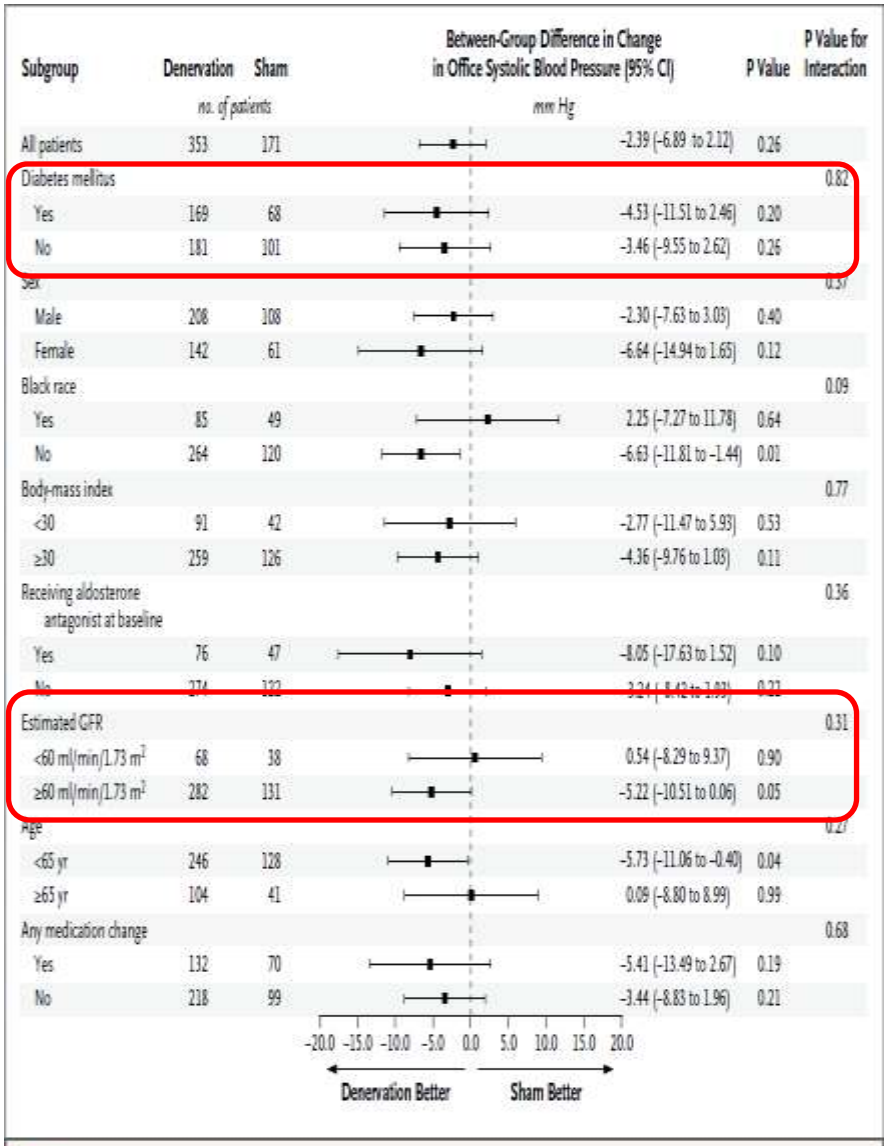


Figure 3. Selected Subgroup Analyses.

Shown are between-group differences in the change in office systolic blood pressure from baseline to 6 months in selected subgroups. The body-mass index is the weight in kilograms divided by the square of the height in meters. GFR denotes glomerular filtration rate.

Conclusion

- **This randomized, sham-controlled, blinded trial did not show a benefit of renal-artery denervation with respect to either of the efficacy end points .**

- **The current trial underscores the importance of conducting blinded trials with sham controls in the evaluation of new medical devices before their clinical adoption.**

Limitations

- **1- Medication adherence could not be confirmed.**
- **More than 50% of patients with resistant hypertension are known to be nonadherent to medications.**

- **2- Follow –up :**
- **The 6-month period from baseline to ascertainment of the primary end point might be too short.**

- **3- An operator learning curve :**
- **No significant difference was observed in outcomes between operators performing five or more procedures and those performing fewer than five procedures.**

- **4- There was no direct measurement to confirm that the renal nerves were in fact denervated by the procedure, because there is no test that can be easily performed in a large trial.**

- **5- The results of this trial are specific to the catheter tested and cannot necessarily be generalized to other denervation systems.**

	Symplicity 1	Symplicity 2	Symplicity 3
Numbers	50	106	535
Controlled	No	Yes	RC Sham Trial (Patients were unaware of whether they underwent renal-artery denervation or renal angiography only (sham control).)
Centers	5 particpating centers in Australia and Europe	24 in Europe, Australia, & New Zealand 16 (67%) were hypertension centres of excellence	88
1ry outcome	Safety and b.p lowering Office based blood pressure	offi ce-based blood pressure to 6 months after randomisation	office systolic blood pressure from baseline to 6 months
2ry outcome	renal noradrenaline spillover and RF	Acute and chronic procedural safety	the change in mean 24-hour ambulatory systolic blood pressure at 6 months.
follow-up	1 year	6 months	6 months
Race	Non- white 4%	Non- White 8%	African American 26%
Dropout	80%		
Randomization		Randomisation; Data analysers were not masked to treatment-group assignment.	2:1 ratio to undergo renal artery denervation or a sham procedure

Questions

- **1) What exactly went wrong for the study SYMPLICITY HTN-3?**
- **2) Is there a need for procedural improvements ?**
- **3) Does renal denervation works ?**
- **4) Is Renal Denervation Dead?**
- **5) is it safe ?**

What exactly went wrong

- The methodology in this study was far, far, far more rigorous than in previous studies.
- 1- It had a sham control . Patients were blinded to whether they received renal denervation or only renal arteriography.
- They were brought into the catheterization laboratory wearing blindfolds, and headphones with music playing.

2- Blood Pressures monitoring: it prospectively looked at blood pressures not only in the office but also at ambulatory blood pressures.

3- There were mandates for the use of spironolactone.

5- There were anatomic criteria that were not present in other studies.

What exactly went wrong? Did Race Play a Role

- In the SYMPLICITY HTN-3 trial, 30% of the patients were African Americans. We know that those patients tend to differ in terms of pathophysiology.

- There's evidence indicating that African Americans have a different pathophysiology in different disease states.

- In heart failure, beta-blockers were not as effective in African Americans as in European or Caucasian people.

What exactly went wrong ?
Hawthorne effect

- Patients modify their behavior because they are being monitored extensively in a clinical trial, might have led some patients to take their medications more diligently than when on their own.

- **Thought of an interventionalist treating hypertension with a catheter "to a man with a hammer, everything looks like a nail."**

Need for procedural improvements ?

- **There is still a need for procedural improvements.**
- **Right now, the biggest problem is that it is impossible for clinicians to know if they have achieved successful denervation of the renal artery.**
- **Number of ablations ? predicted a reduction in systolic blood pressure in the renal denervation group.**
- **An increasing number of ablations was associated with a consistent and progressive reduction in systolic blood pressure.**
- **“Circumferentiality" of the renal denervation procedure ?.**

Does renal denervation work ?

- **No question about it.**
- **It wouldn't be around today if it didn't.**
- **It's been studied for over 40 years. It definitely works, but in the absence of anything else !!!!!!!!!!.**

Is The Renal Denervation Dead?

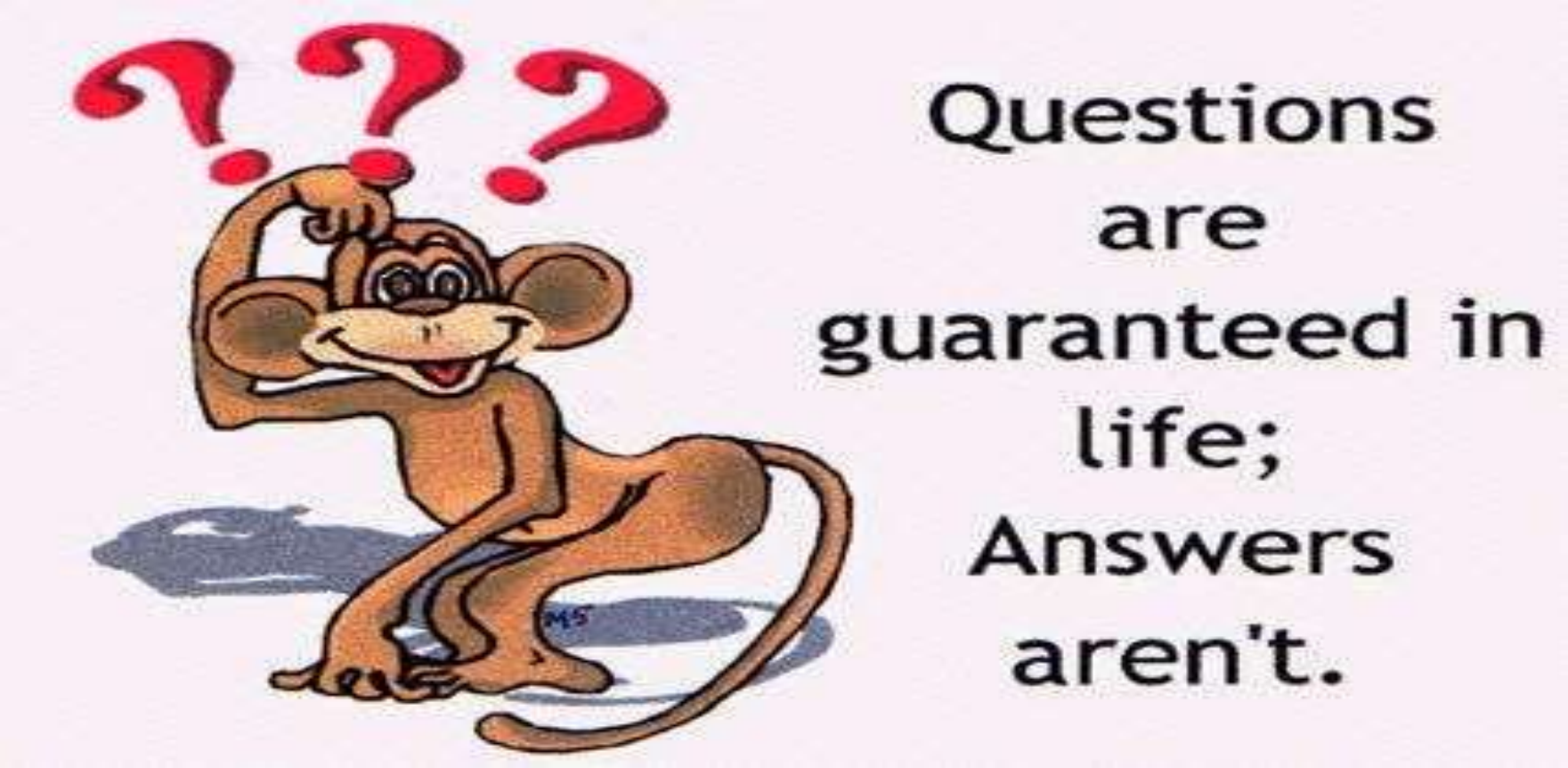
- **The negative result from Symplicity brings the renal-denervation train to a grinding halt.“**
- **NO, renal denervation is NOT "dead" but rather needs a "reboot," .**
- **Getting back to basics in terms of better understanding the anatomy, neurology, and physiology of the procedure.**
- **leave the door open for renal denervationas it is not just a crack.**

*Expanded results presented at the *American College of Cardiology Annual Meeting 2012* (Krum, H.)

Is it Safe ?

- **Despite the lack of effect on blood pressure in SYMPLICITY HTN-3, there were no safety concerns raised during the trial.**

Unanswered Questions



Medtronic

SYMPLICITY HTN U.S. Trial Program

Caution: Investigational device. Limited by United States law to investigational use.

The SYMPLICITY HTN-4 Clinical Trial

The SYMPLICITY HTN-4 clinical trial is very similar to the SYMPLICITY HTN-3 Clinical trial. The purpose of both studies is to provide additional information about a medical device intended to help treat high blood pressure in people whose blood pressure is not controlled despite treatment with multiple blood pressure medications. The primary difference between SYMPLICITY HTN-3 and SYMPLICITY HTN-4 is reflected in the population being studied: SYMPLICITY HTN-3 is investigating the efficacy and safety of renal denervation in volunteers who have an office systolic blood pressure reading above 160 mmHg, whereas SYMPLICITY HTN-4 is investigating the efficacy and safety of renal denervation in volunteers who have an office systolic blood pressure between 140 and 160 mmHg.

	SYMPLICITY HTN-3	SYMPLICITY HTN-4
Randomized	Yes	Yes
Controlled	Yes	Yes
Blinded	Yes	Yes
[illegible]	[illegible]	[illegible]
Number of Centers Participating	Up to 90 in the US	Up to 100 in the US
Blood Pressure Required for Inclusion	> 160 mmHg Systolic	140-160 mmHg Systolic

If you decide to participate in this study, the potential risks and benefits will be thoroughly explained, and you will have the opportunity to discuss participation both with research staff and your family. If selected, your current blood pressure medications (total daily doses and medication types) will not be changed unless medically necessary. In addition to your current blood pressure medications, you may receive treatment with this investigational therapy.

...

Learn more about this investigational therapy and our clinical trial. To see if you may qualify for this clinical trial, please take this short survey or connect with a participating doctor.

Talk with your doctor about potential risks associated with renal denervation.

Am I a Candidate?

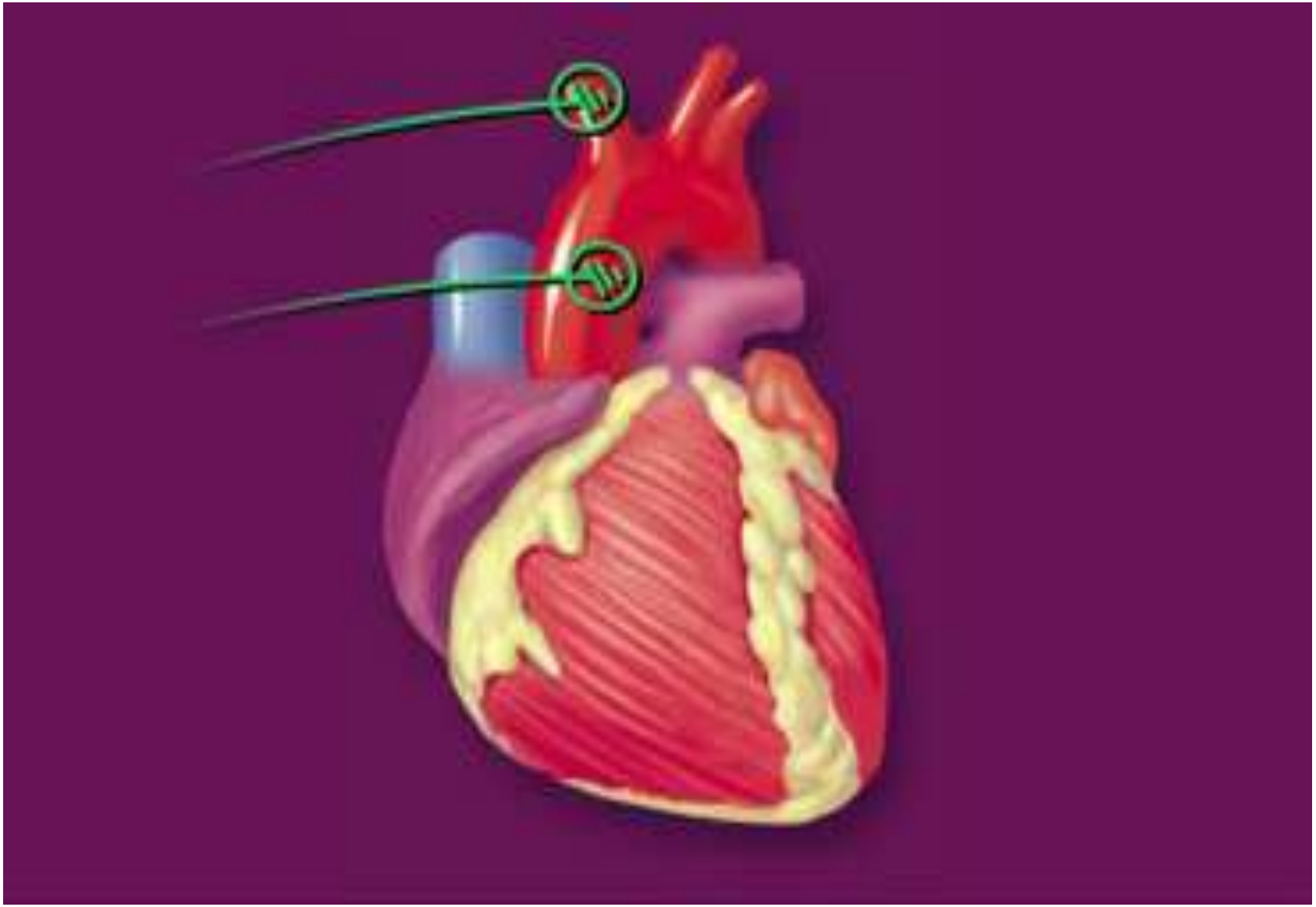
Find a Study Doctor

Important Safety Information

About Medtronic

Useful Links

3- Baroreflex Activation Therapy



The device


Medscape
Programming System
Implantable Pulse Generator
Source: Pacing Clin Electrophysiol © 2011 Blackwell Publishing

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Hypertension

Novel Baroreflex Activation Therapy in Resistant Hypertension

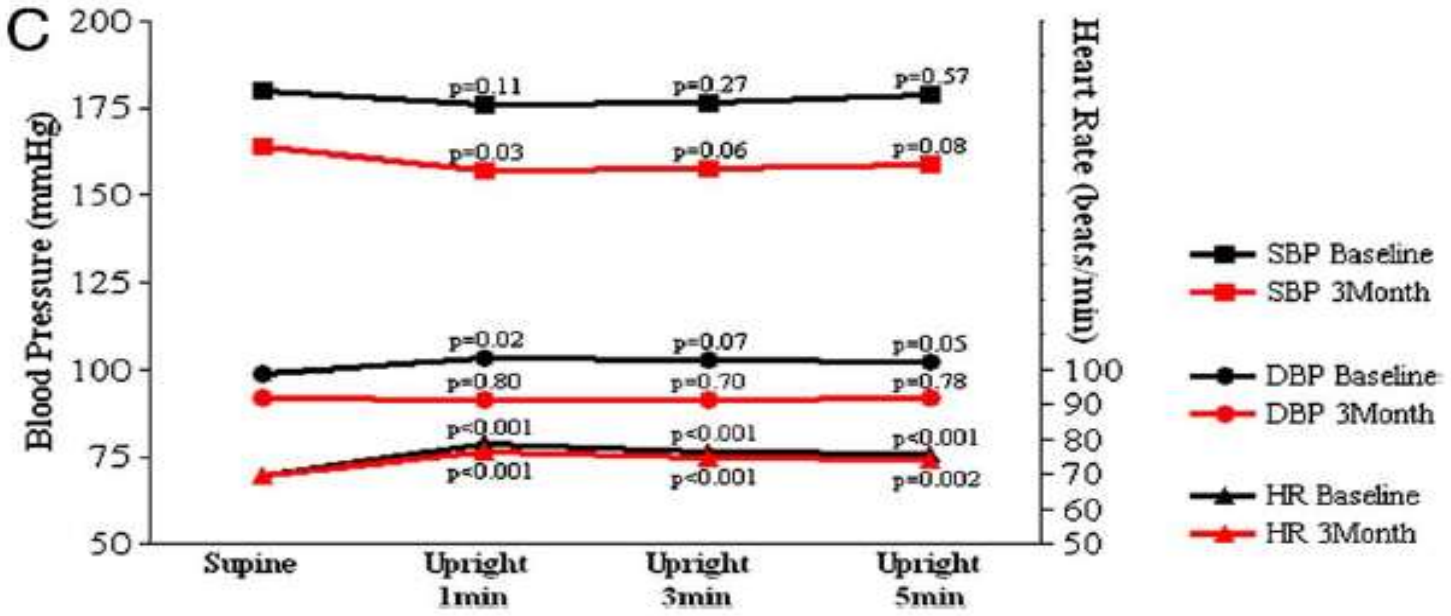
Results of a European Multi-Center Feasibility Study

Device-Based Therapy in Hypertension (DEBuT-HT) trial

Device-Based Therapy in Hypertension (DEBuT-HT) trial

Functional Safety Results After 3 Months and 1 Year of Device Therapy

- 45 patients with resistant hypertension were enrolled during year 2004–2007 and were followed up over the next 2 years



After 3 months of BAT :
Mean office BP was reduced by 21/12 mmHg and ABPM was reduced by 6/4 mmHg.

Device-Based Therapy in Hypertension (DEBuT-HT) trial

Office blood pressure	n = 37	n = 26	n = 17
SBP, mm Hg	−21 ± 4 (p < 0.001)	−30 ± 6 (p < 0.001)	−33 ± 8 (p = 0.001)
DBP, mm Hg	−12 ± 2 (p < 0.001)	−20 ± 4 (p < 0.001)	−22 ± 6 (p = 0.002)
HR, beats/min	−8 ± 2 (p < 0.001)	−8 ± 2 (p = 0.001)	−11 ± 4 (p = 0.008)
Ambulatory blood pressure	**n = 26**	**n = 15**	**n = 8**
SBP, mm Hg	−6 ± 3 (p = 0.102)	−13 ± 3 (p < 0.001)	−24 ± 8 (p = 0.017)
DBP, mm Hg	−4 ± 2 (p = 0.041)	−8 ± 2 (p = 0.001)	−13 ± 5 (p = 0.049)
HR, beats/min	−5 ± 2 (p = 0.001)	−6 ± 2 (p = 0.012)	−11 ± 34 (p = 0.005)

Blood Pressure Results, Mean Change (Δ) Presented for Office and Ambulatory Readings

(DEBuT-HT) trial
Limitations and AE

- Not randomized
- Involved medication changes during the study period.
- Some serious adverse events were also reported;
- 3 infections required the device to be explanted
- 1 perioperative stroke with minimal residual effects, probably due to intra-operative injury to the hypoglossal nerve.
- 1 Device-related severe adverse effect was the movement of implantable pulse generator requiring repositioning.

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doi:10.1016/j.jacc.2011.06.008

EXPEDITED PUBLICATION

Baroreflex Activation Therapy Lowers Blood Pressure in Patients With Resistant Hypertension

Results From the Double-Blind, Randomized, Placebo-Controlled Rheos Pivotal Trial

John D. Bisognano, MD, PHD,* George Bakris, MD,† Mitra K. Nadim, MD,‡ Luis Sanchez, MD,§ Abraham A. Kroon, MD, PHD,‖ Jill Schafer, MS,¶ Peter W. de Leeuw, MD, PHD,‖ Domenic A. Sica, MD#

Rochester, New York; Chicago, Illinois; Los Angeles, California; St. Louis, Missouri; Maastricht, the Netherlands; Minneapolis, Minnesota; and Richmond, Virginia

Double-blind randomized trial of 265 subjects with resistant hypertension.

Rheos Pivotal trial
End Points

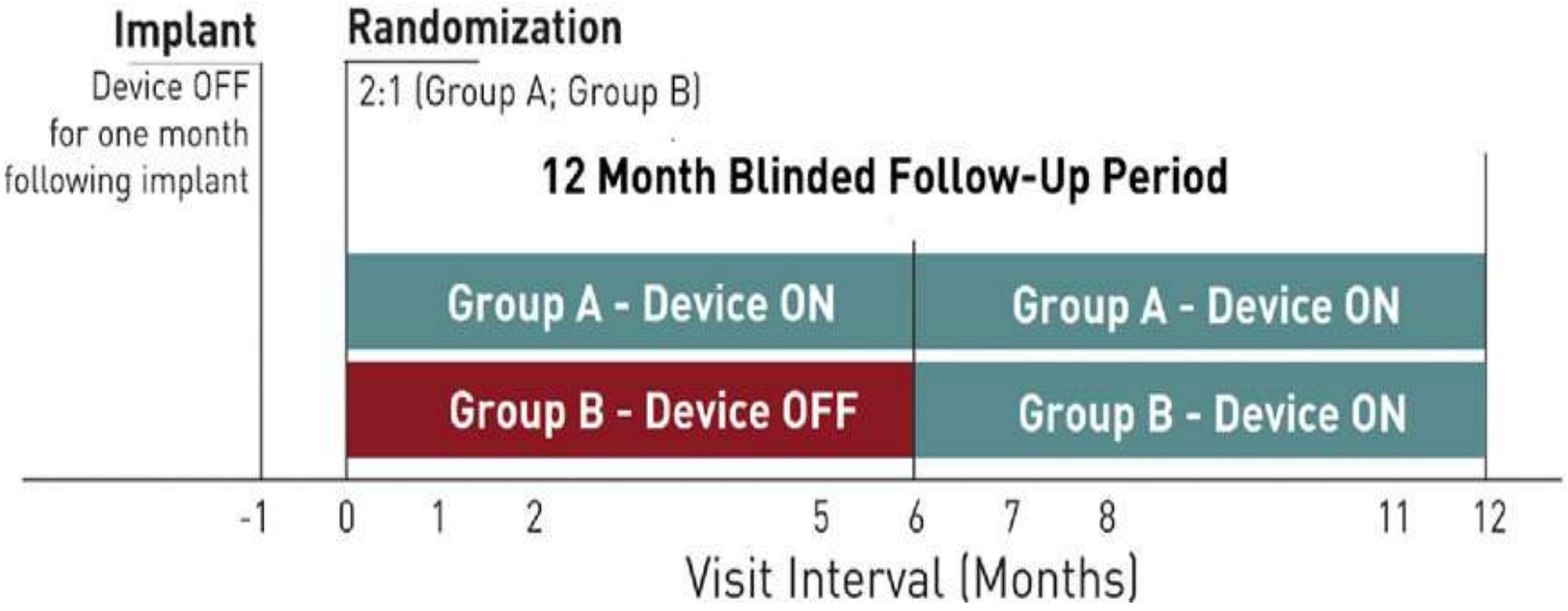
- **5 pre-specified coprimary endpoints, 2 for efficacy and 3 for safety, as follows:**

- **1) Acute efficacy**
- **2) Sustained efficacy**
- **3) Procedural safety**
- **4) BAT safety**
- **5) Device safety**

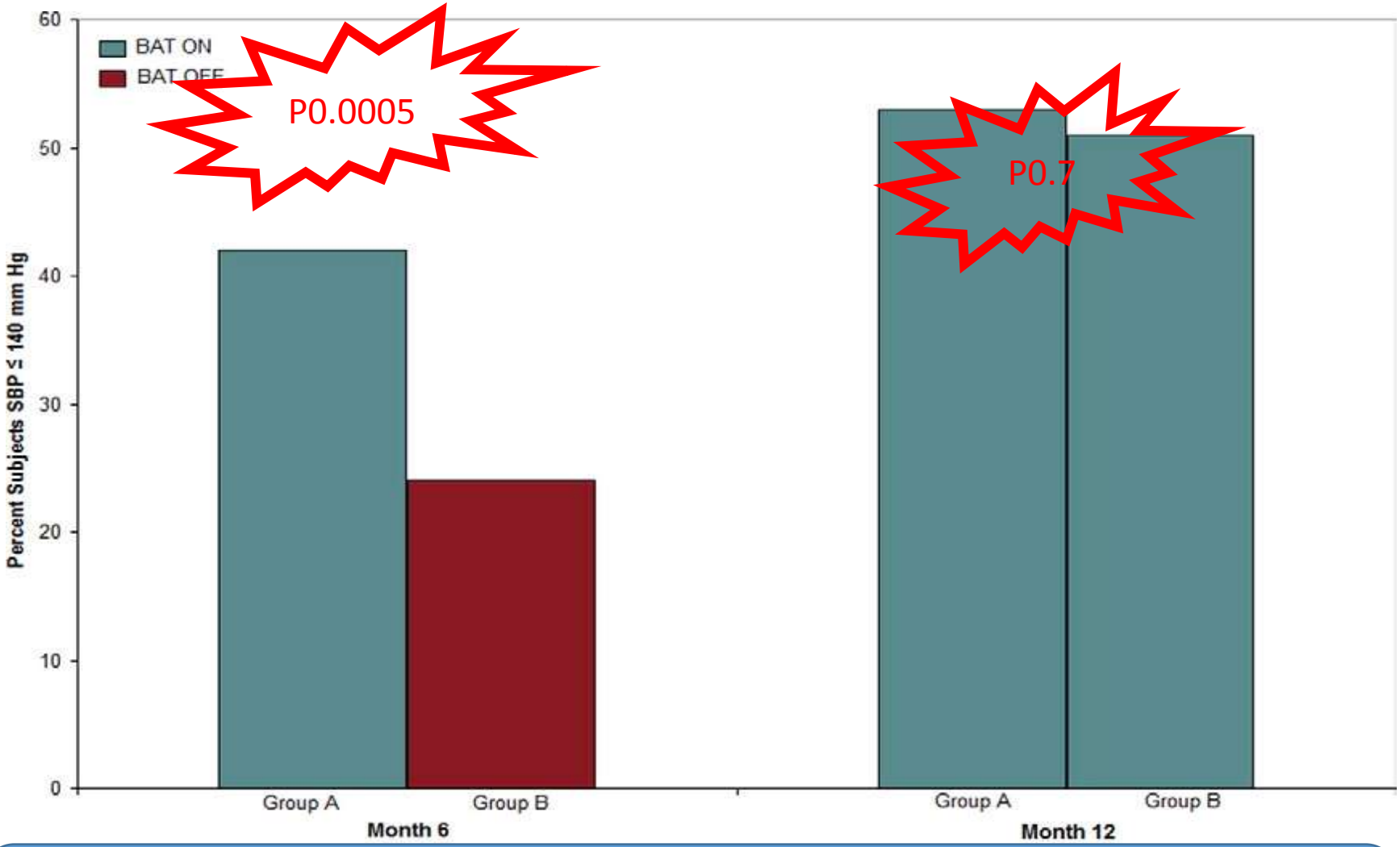
Rheos Pivotal trial
Baseline Characterestics

	Group A (n = 181)	Group B (n = 84)
Sex		
Male	116 (64%)	46 (55%)
Female	65 (36%)	38 (45%)
Age, yrs	53.7 ± 10.5	52.4 ± 9.8
Race		
Caucasian	146 (81%)	59 (70%)
Black	30 (17%)	18 (21%)
BP, mm Hg		
Systolic	169 ± 26	168 ± 24
Diastolic	101 ± 17	100 ± 14
Heart rate, beats/min	79 ± 14	79 ± 17
Body mass index, kg/m^2	32.6 (5.4%)	32.2 (5.9%)
Diabetes	57 (31%)	29 (35%)
Previous CAD	38 (21%)	18 (21%)
Heart failure	12 (7%)	10 (12%)
Previous stroke	24 (14%)	9 (11%)
Number of BP medications	5.2 (1.6)	5.2 (1.8)
BP medications		
≤3	23 (13%)	13 (16%)
4	40 (22%)	22 (26%)
≥5	118 (65%)	49 (58%)

Rheos Pivotal trial
Trial Schema



Proportion of Subjects That Achieved SBP ≤140 mm Hg



A significant difference is observed between the 2 groups at 6 months and no difference is observed at 12 months when both groups have received BAT for at least 6 months.

Observed Mean Change in SBP

a decrease in SBP of 26 30 mm Hg for Group A and 17 29 mm Hg for Group B (p 0.03) at 6 months and a decrease of 35 28 mm Hg for Group A and 33 30 mm Hg for Group B (p 0.57) at 12 months.

Table 3 Summary of Adverse Events

Procedural	68 (25.5)
Surgical complication	13 (4.8)
Nerve injury with residual	13 (4.8)
Device	34 (12.8)
Hypertension-related stroke	6 (2.3)

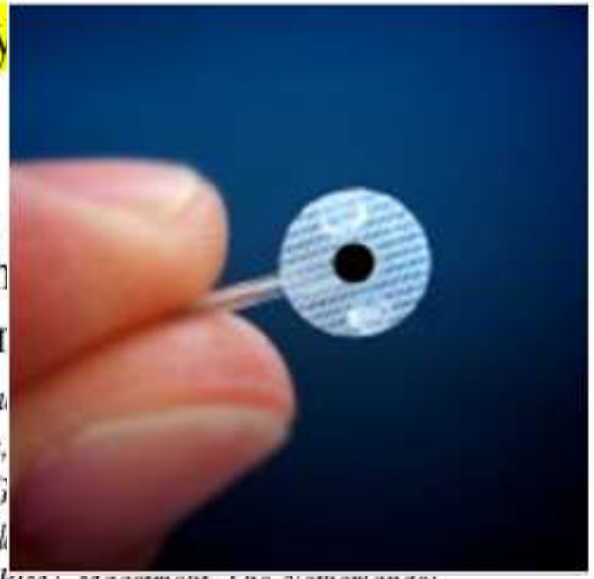
Conclusions A clinically meaningful measure, those achieving a SBP of ≤140 mm Hg, yielded a significant difference between the groups. The weight of the overall evidence suggests that over the long-term, BAT can safely reduce SBP in patients with resistant hypertension. Future clinical trials will address the limitations of this study and further define the therapeutic benefit of BAT. (J Am Coll Cardiol 2011;58:765–73) © 2011 by the American College of Cardiology Foundation

Bisognano et al., J Am Coll Cardiol. 2011;58(7):765–73

Journal of the American Society of Hypertension 6(4) (2012) 270–276

Research Article

Minimally invasive system for baroreflex activation therapy chronically with pacemaker-like safety the Barostim *neo* trial



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Journal of the American Society of Hypertension 6(4) (2012) 270–276

Research Article

Minimally invasive system for baroreflex activation therapy chronically lowers blood pressure with pacemaker-like safety profile: results from the Barostim *neo* trial

- **Minimally invasive system, the following adjustments were made:**
- **1) lead implantation required unilateral carotid sinus exposure only, which could be performed via a small incision (2.5–5 cm) because of the reduced size of the lead.**

- **2) Carotid sinus exposure involved dissection of the internal carotid artery and did not require surgical exposure of the external carotid artery.**

Journal of the American Society of Hypertension 6(4) (2012) 270–276

Research Article

Minimally invasive system for baroreflex activation therapy chronically lowers blood pressure with pacemaker-like safety profile: results from the Barostim *neo* trial

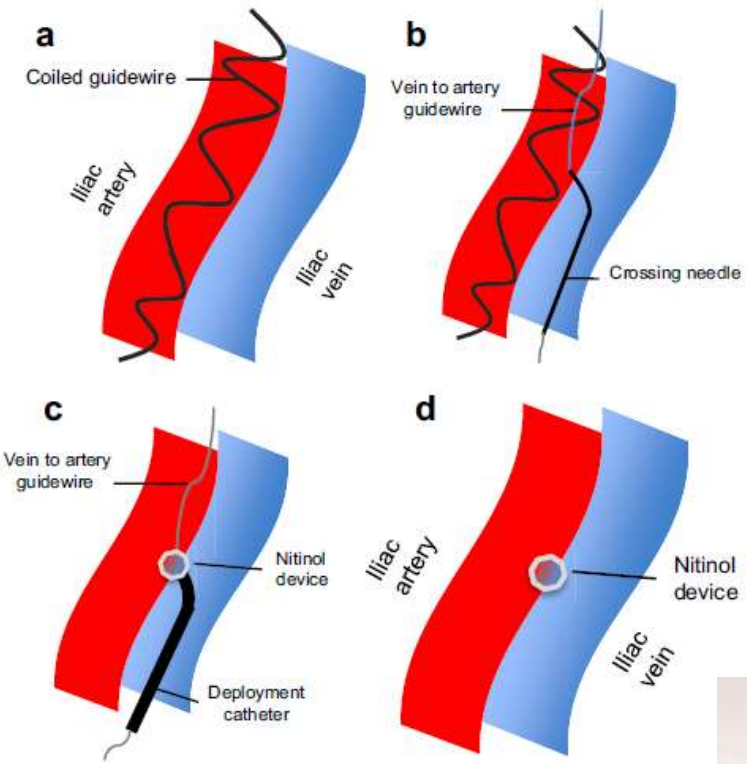
System- or procedure-related complications

Event	Days From Implant	Procedure-related	System-related	Status	Patients Free From Events (%)
Perioperative events					90%
Device pocket hematoma	3	Yes	No	Recovered, no residual effects	
Self-inflicted wound complication	7	Yes	No	Recovered, no residual effects	
Intermittent pain lateral of device system	30	Yes	No	Recovered, no residual effects	
Long-term events					97%
Intermittent pain near the device system	44	Yes	No	Recovered, no residual effects	

Rheos Pivotal trial VS Barostem Neo Trial

Study	Rheos Trial	Barostim Neo Trial
Design	Double-blind randomized trial .	Nonrandomized, open-label European Union and Canada (seven centers (6 EU, 1 Canada)).
Patients	265 subjects	Thirty patients
The primary efficacy objective	5 Objectives	Reductions in office cuff systolic BP through 6 months of BAT relative to baseline BP
The primary safety objective		all system- and procedure-related complications through the study 6-month visit.
Unilateral therapy	None	75%
30 days System or Procedure Free event	75%	90%
procedure implant time (min)	196 min	107 Min
long-term safety profile of BAT	87%	97 %
systolic BP reductions 6 months	26 mm Hg	21 mm Hg
Ambulatory BP measurements	Yes	No

Central AV Anastomosis


a
Coiled guidewire
Iliac artery
Iliac vein
b
Vein to artery guidewire
Crossing needle
c
Vein to artery guidewire
Nitinol device
Deployment catheter
d
Iliac artery
Nitinol device
Iliac vein

Central AV Anastomosis

- ROX Medical arteriovenous (AV) coupler is a stent-like device made of nickel/titanium alloy (nitinol) that exhibits shape memory to self-expand on deployment into a pre-formed configuration.

- It is deployed via percutaneous trans-arterial and -venous access from the external iliac vein into the adjacent external iliac artery, just above the level of the femoral head, to form a fixed diameter AV anastomosis delivering an arterial–venous shunt estimated to be ~0.8–1 L/ min when sized to 4 mm in diameter .

Central AV Anastomosis

Creation of an iliac arteriovenous shunt lowers blood pressure in chronic obstructive pulmonary disease patients with hypertension

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Objective: Vasodilators are used with caution in patients with chronic obstructive pulmonary disease (COPD). We have developed a device for percutaneous arteriovenous shunt creation in the iliac region to increase cardiac output and oxygen delivery for patients with COPD. Although this device does not cause significant blood pressure changes in normotensive patients with COPD, we hypothesized that arteriovenous shunt creation might cause vasodilator effects in hypertensive patients because of a reduction in vascular resistance.

Methods: Twenty-four patients with COPD and hypertension enrolled in an open label study of arteriovenous shunt creation for COPD. We performed cardiac catheterization at baseline and again 3 to 6 months after the procedure. As a safety measure we also recorded office blood pressure at baseline and again after 3, 6, 9, and 12 months.

Results: The procedure increased oxygen delivery (1.1-1.4 $L.min^{-1}$) and cardiac output (6-8.2 $L.min^{-1}$) ($P < .001$) and lowered both the systemic vascular resistance ($P < .001$) and the pulmonary vascular resistance ($P < .01$). After 12 months, however, the average systolic blood pressure was reduced from 145 to 132 mm Hg ($P < .0001$), and the average diastolic blood pressure was reduced from 86 to 67 mm Hg ($P < .0001$).

Conclusions: Percutaneous iliac arteriovenous fistula creation for COPD causes a significant and persistent lowering of blood pressure in patients with co-existing hypertension. (J Vasc Surg 2014;59:1078-83.)

Central AV Anastomosis

- Significant fall in BP due to:
  - ↓ VR, ↑ COP.
  - Enhanced tissue O2 delivery → ↓ sympathetic overactivity
  - ↓ cardiac load
- Incorporating a segment of vein in the central arterial circuit to restore the is expected to cause an immediate reduction of blood pressure through improved arterial compliance .
- Increased flow to the cardio-pulmonary circuit will stimulate release of atrial natriuretic peptide : a potent vasorelaxant peptide that additionally has tubular effects in the glomerulus to reduce sodium reabsorption .
- increased cardiac output resulting in stimulation of right atrial baroreceptors (via the Bainbridge reflex) and possibly cardiac vagal mechanoreceptors (via increased parasympathetic tone)may cause a beneficial sympathomodulatory effect on natriuresis and vasomotor tone .

Central arteriovenous anastomosis for the treatment of patients with uncontrolled hypertension (the ROX CONTROL HTN study): a randomised controlled trial

*Melvin D Lobo, Paul A Sobotka, Alice Stanton, John R Cockcroft, Neil Sulke, Eamon Dolan, Markus van der Giet, Joachim Hoyer, Stephen S Furniss, John P Foran, Adam Witkowski, Andrzej Januszewicz, Danny Schoors, Konstantinos Tsioufis, Benno J Rensing, Benjamin Scott, G André Ng, Christian Ott, Roland E Schmieder, for the ROX CONTROL HTN Investigators**

Summary

Background Hypertension contributes to cardiovascular morbidity and mortality. We assessed the safety and efficacy of a central iliac arteriovenous anastomosis to alter the mechanical arterial properties and reduce blood pressure in patients with uncontrolled hypertension.

Methods We enrolled patients in this open-label, multicentre, prospective, randomised, controlled trial between October, 2012, and April, 2014. Eligible patients had baseline office systolic blood pressure of 140 mm Hg or higher and average daytime ambulatory blood pressure of 135 mm Hg or higher systolic and 85 mm Hg or higher diastolic despite antihypertensive treatment. Patients were randomly allocated in a 1:1 ratio to undergo implantation of an arteriovenous coupler device plus current pharmaceutical treatment or to maintain current treatment alone (control). The primary endpoint was mean change from baseline in office and 24 h ambulatory systolic blood pressure at 6 months. Analysis was by modified intention to treat (all patients remaining in follow-up at 6 months). This trial is registered with ClinicalTrials.gov, number NCT01642498.

Findings 83 (43%) of 195 patients screened were assigned arteriovenous coupler therapy (n=44) or normal care (n=39). Mean office systolic blood pressure reduced by 26·9 (SD 23·9) mm Hg in the arteriovenous coupler group (p<0·0001) and by 3·7 (21·2) mm Hg in the control group (p=0·31). Mean systolic 24 h ambulatory blood pressure reduced by 13·5 (18·8) mm Hg (p<0·0001) in arteriovenous coupler recipients and by 0·5 (15·8) mm Hg (p=0·86) in controls. Implantation of the arteriovenous coupler was associated with late ipsilateral venous stenosis in 12 (29%) of 42 patients and was treatable with venoplasty or stenting.

Interpretation Arteriovenous anastomosis was associated with significantly reduced blood pressure and hypertensive complications. This approach might be a useful adjunctive therapy for patients with uncontrolled hypertension.

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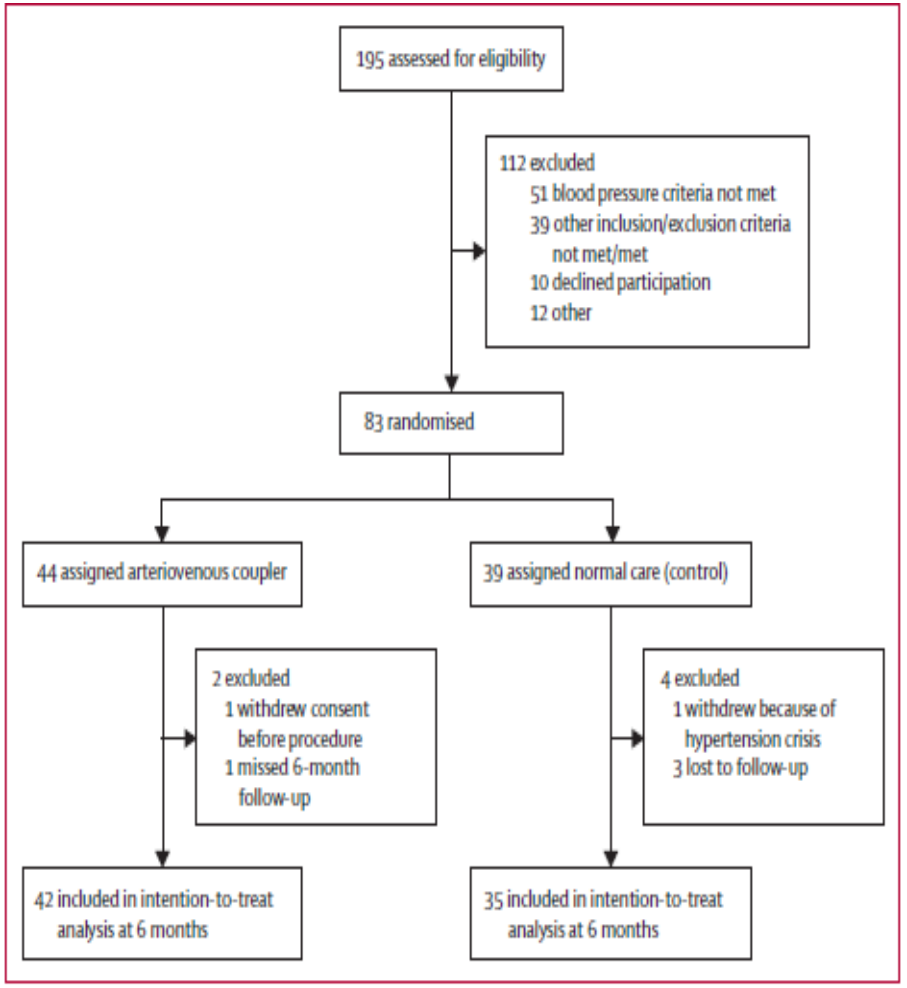
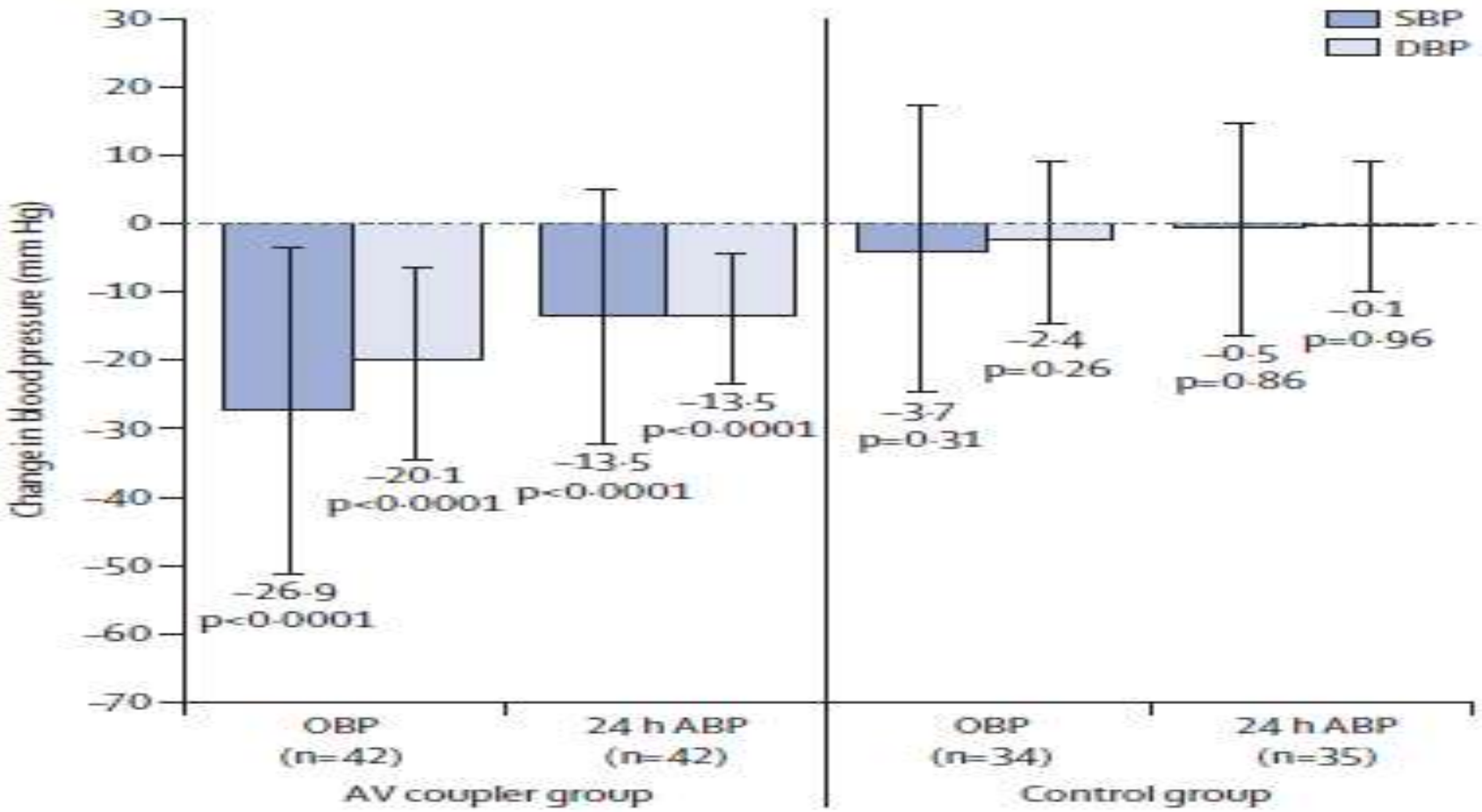
ROX control HT

- An international, open-label, 16 multicentre, prospective, randomised, controlled trial .
- 83 patients were randomized in a 1:1 fashion to receive standard care (medication continuation) or insertion of the AV coupler plus standard care .
- co-primary endpoint analysis (OBP and ABP) at 6 months.



ROX control HT



Rox control HT

- **Anti Hypertensives reduction:**
- **11 patients in the arteriovenous coupler group compared with only two in the control group (p=0·03).**

- **Estimated glomerular filtration rate :**
- **No significant mean change from baseline in the arteriovenous coupler (–1·8 [SD 9·0] mL/min per 1·73 m^2) or control group (1·9 [7·6] mL/min per 1·73 m^2) at 6 months.**

Adverse events related to arteriovenous coupler placement or device

	Number (%) of adverse events (n=42)
Procedural complication	

Interpretation Arteriovenous anastomosis was associated with significantly reduced blood pressure and hypertensive complications. This approach might be a useful adjunctive therapy for patients with uncontrolled hypertension.

Deep venous thrombosis	1 (2-4%)
Lower limb pain	1 (2-4%)
Device-related event	
Venous stenosis	12 (28-6%)

*Coupler retrieved via arterial sheath and second coupler successfully deployed.

The Take-Home Message

- **Catheter-based renal denervation in patients with treatment-resistant essential hypertension, resulted in significant reductions in office BP, .However the technique still need more and more justification.**

- **Baroreceptor activation therapy is among the most evaluated device-based therapy for resistant hypertension; however, more randomized and validated data are needed with an improvement in safety profiles.**

- **Formation of a central AV anastomosis via a proprietary anastomotic coupler device has joined the burgeoning suite of interventional strategies for the reduction of BP in RHTN.**


Thank you